

A Consensus Model of Glucose-Stimulated Insulin Secretion in the Pancreatic β -Cell

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ABSTRACT

The pancreas plays a critical role in maintaining glucose homeostasis through the secretion of hormones from the islets of Langerhans. Glucose-stimulated insulin secretion (GSIS) by the pancreatic β -cell is the main mechanism for reducing elevated plasma glucose. Here we present a systematic modeling workflow for the development of kinetic pathway models using the Systems Biology Markup Language (SBML). Steps include retrieval of information from databases, curation of experimental and clinical data for model calibration and validation, integration of heterogeneous data including absolute and relative measurements, unit normalization, data normalization, and model annotation. An important factor was the reproducibility and exchangeability of the model, which allowed the use of various existing tools. The workflow was applied to construct the first consensus model of GSIS in the pancreatic β -cell based on experimental and clinical data from 39 studies spanning 50 years of pancreatic, islet, and β -cell research in humans, rats, mice, and cell lines. The model consists of detailed glycolysis and equations for insulin secretion coupled to cellular energy state (ATP/ADP ratio). Key findings of our work are that in GSIS there is a glucose-dependent increase in almost all intermediates of glycolysis. This increase in glycolytic metabolites is accompanied by an increase in energy metabolites, especially ATP and NADH. One of the few decreasing metabolites is ADP, which, in combination with the increase in ATP, results in a large increase in ATP/ADP ratios in the β -cell with increasing glucose. Insulin secretion is dependent on ATP/ADP, resulting in glucose-stimulated insulin secretion. The observed glucose-dependent increase in glycolytic intermediates and the resulting change in ATP/ADP ratios and insulin secretion is a robust phenomenon observed across data sets, experimental systems and species. Model predictions of the glucose-dependent response of glycolytic intermediates and insulin secretion are in good agreement with experimental measurements. Our model predicts that factors affecting ATP consumption, ATP formation, hexokinase, phosphofructokinase, and ATP/ADP-dependent insulin secretion have a major effect on GSIS. In conclusion, we have developed and applied a systematic modeling workflow for pathway models that allowed us to gain insight into key mechanisms in GSIS in the pancreatic β -cell.

Keywords: glucose-stimulated insulin secretion, GSIS, glycolysis, pancreas, kinetic model, systems biology

1 INTRODUCTION

1 The pancreas plays a vital role in maintaining
2 glucose homeostasis (Woods et al., 2006) through
3 the secretion of hormones from the islets of

Langerhans. The most important hormones are 4
insulin, secreted by the pancreatic β -cells, and 5
glucagon, secreted by the α -cells, both of which play 6

7 key roles in regulating glucose homeostasis (König
8 et al., 2012a).

9 Glucose-induced insulin secretion (GSIS) is
10 a physiological process by which the pancreas
11 releases insulin in response to an increase in blood
12 glucose levels. When glucose enters the bloodstream
13 after a meal, it is taken up by β -cells in the
14 pancreas through glucose transporters, primarily
15 GLUT2 (MacDonald et al., 2005). Once inside the
16 β -cells, glucose is metabolized via glycolysis, which
17 produces energy in the form of ATP.

18 The coupling of glycolysis with the insulin
19 secretion mechanism in the β -cell is established by
20 the regulatory effects of glycolytic intermediates
21 on the levels of energy metabolites such as ATP
22 and NADH (Newsholme et al., 2014; Prentki
23 et al., 2013). The rise in ATP levels triggers
24 a series of events that lead to the release of
25 insulin. Specifically, the high ATP levels close
26 ATP-sensitive potassium channels (Ashcroft, 2006),
27 which leads to depolarization of the cell membrane
28 and opening of voltage-gated calcium channels. The
29 influx of calcium triggers the exocytosis of insulin-
30 containing vesicles, leading to the release of insulin
31 into the bloodstream (Rorsman and Braun, 2013;
32 Guerrero-Hernandez and Verkhatsky, 2014). The
33 K_{ATP}/Ca^{2+} independent signaling mechanisms
34 and the other metabolites besides glucose contribute
35 to the amplification of the signaling events that
36 trigger insulin secretion (Guay et al., 2013).

37 GSIS by the pancreatic β -cell is the primary
38 mechanism for lowering elevated plasma glucose
39 levels. The amount of insulin released increases
40 with the glucose in the bloodstream. This process
41 is crucial for the regulation of blood glucose levels
42 by promoting the uptake and use of glucose by cells
43 throughout the body, such as muscle, fat tissue, and
44 the liver (Di Camillo et al., 2014; Fritsche et al.,
45 2008).

46 Glycolysis is the primary metabolic pathway
47 responsible for GSIS. It involves the uptake of
48 glucose and its conversion to pyruvate, which is
49 critical for ATP synthesis and maintenance of ATP
50 levels. Experimental data from metabolic profiling

studies in islet cells support the key role of glycolysis 51
in GSIS (Spégel et al., 2013, 2015; Taniguchi et al., 52
2000). As glucose levels increase, glycolytic flux 53
and most glycolytic intermediates increase in a dose- 54
dependent manner. Changes in adenine nucleotide 55
levels due to variations in glycolytic flux lead 56
to changes in nucleotide ratios, with increasing 57
glucose levels resulting in a positive correlation 58
between the ATP/ADP ratio and Ca^{2+} response 59
and insulin release. This trend is consistent across 60
several studies (Detimary et al., 1996; Malaisse 61
et al., 1978; Salvucci et al., 2013), including isolated 62
islets perfused with glucose, rat and mouse tissue 63
homogenates, and insulin-secreting cell lines. The 64
increase in ATP/ADP ratio ranges from 2 to 7 65
when glucose levels are increased from 2.8mM 66
to 30mM, indicating similar behavior in different 67
experimental systems studying insulin secretion by 68
the pancreas (Huang and Joseph, 2014). 69

Mathematical models have been developed 70
to investigate the metabolic and signaling 71
mechanisms that trigger and amplify insulin 72
secretion. Early models of β -cells focused on 73
examining the relationship between glycolytic 74
oscillations and pulsatile insulin release to 75
understand GSIS (Bertram et al., 2007; Tornheim, 76
1997). Merrins et al. analyzed the oscillations in 77
glycolytic intermediates (i.e. fructose-6-phosphate, 78
fructose-2,6-bisphosphate, and fructose-1,6- 79
bisphosphate) and their effect on pulsatile insulin 80
secretion (Merrins et al., 2012), while other models 81
integrated glycolytic flux with mitochondrial ATP 82
production to study the role of reducing equivalents 83
such as pyridine nucleotides in enhancing insulin 84
secretion (Westermarck et al., 2007; Bertram et al., 85
2006). Jiang et al. further combined previously 86
developed models of glycolysis, citric acid cycle, β - 87
oxidation, pentose phosphate shunt, and respiratory 88
chain and studied the local and global dynamics 89
of the GSIS mechanism in response to parameter 90
perturbations. These models were coupled with the 91
calcium signaling pathway of Fridlyand et al. to 92
create an integrated metabolic model (Fridlyand 93
and Philipson, 2010; McKenna et al., 2016). 94

95 To investigate the synergistic insulinotropic effect
96 of other nutrient sources, Salvucci et al. (Salvucci
97 et al., 2013) developed a model by integrating
98 alanine metabolism with glucose metabolism, the
99 citric acid cycle, and the respiratory chain. Gelbach
100 et al. developed a system of 65 reactions integrating
101 glycolysis, glutaminolysis, the pentose phosphate
102 pathway, the citric acid cycle, the polyol pathway,
103 and the electron transport chain to study the kinetics
104 of insulin secretion (Gelbach et al., 2022).

105 However, the majority of these models are based
106 on earlier models that were developed using kinetic
107 data from organisms other than humans or non-
108 pancreatic tissues, such as a glycolysis model that
109 utilized kinetic data from experiments on yeast cell
110 extract, or a glycolysis model based on kinetic data
111 from mammalian muscle (Smolen, 1995). Often,
112 the data used to build these models is limited and
113 comes from a single experimental study. In most
114 models specific to β -cells, reaction kinetics are
115 described by simple mass-action rate laws. There
116 exists no detailed kinetic model of the changes
117 in glycolysis during GSIS that can effectively
118 integrate the observed changes in glycolytic and
119 energy intermediates from a wide range of GSIS
120 experiments.

121 In systems biology and systems medicine,
122 ensuring the reproducibility of computational
123 models and integrating diverse data from
124 multiple sources into these models are critical
125 challenges. Standards for model description,
126 such as the Systems Biology Markup Language
127 (SBML) (Hucka et al., 2015; Keating et al., 2020),
128 have been developed to enable the reusability
129 and reproducibility of existing models, but they
130 have yet to be utilized in the field of pancreatic
131 GSIS modeling. Furthermore, there is a need to
132 address how to integrate heterogeneous data from
133 different studies conducted in different organisms
134 and experimental systems in the context of GSIS
135 modeling.

136 This study aims to develop a detailed kinetic model
137 of GSIS and the associated changes in glycolysis in
138 the pancreatic β -cell. The novel contributions of this

work include a systematic curation and integration
of changes in glycolytic metabolites from different
experimental studies across different species and
experimental systems. Based on this unique data
set, a detailed kinetic model of glycolysis and GSIS
was constructed using a systematic approach with a
focus on reproducibility. This approach allowed the
establishment of a consensus model of the changes
that occur in insulin secretion with varying glucose
concentrations. The overall goal was to provide a
better understanding of the mechanisms underlying
GSIS and to contribute to the development of
improved computational models of these processes.

2 RESULTS

Our study introduces a detailed kinetic model of
GSIS in the pancreatic β -cell, which has the ability
to simulate alterations in glycolytic intermediates
and ATP/ADP ratio due to glucose levels and the
effect of change in the energy state of the β -cell on
insulin secretion.

2.1 Systematic curation of data set of changes in GSIS

In the course of this study, we compiled a
comprehensive data set (Tab. 1) of GSIS based
on experimental and clinical data from 39 studies
spanning half a century of research on pancreatic,
islet, and β -cell function in humans, rats, mice,
and cell lines. Specifically, we systematically
curated metabolomics data from studies conducted
between 1970 and 2020, comprising information
on the concentration of glycolytic intermediates
and cofactors in both time-course and steady-
state experiments, as well as the corresponding
glucose doses. The data set contains 17 metabolites,
comprising 359 data points from steady-state
experiments and 249 data points from time-course
studies. It includes both absolute and relative
measurements of metabolite changes, and an
overview of the available information for each
metabolite and study is presented in Fig. 1.

This data set represents the first open and
FAIR (findable, accessible, interoperable, and

180 reusable) large-scale collection of data on changes in
181 glycolysis and insulin secretion in the pancreatic β -
182 cell during GSIS. We used the absolute and relative
183 measurements of glycolysis metabolites and insulin
184 secretion rates in this data set for model calibration
185 and evaluation.

186 The data set is available under a CC-BY4.0 license
187 from [https://github.com/matthiaskoenig/pancreas-](https://github.com/matthiaskoenig/pancreas-model)
188 [model](https://github.com/matthiaskoenig/pancreas-model).

189 2.2 Reproducible modeling workflow

190 In this study, we describe a comprehensive
191 modeling workflow for building small kinetic
192 pathway models (Fig. 2) using SBML (Hucka et al.,
193 2015; Keating et al., 2020).

194 In our model-building workflow, we followed
195 several steps to construct a kinetic SBML model
196 of glycolysis. A) First, we built an SBML model
197 based on glycolytic reactions and intermediates from
198 existing models and pathway databases. B) We then
199 annotated metabolites and reactions with metadata
200 information which was extended by querying VMH
201 and the BiGG database, resulting in mappings
202 to additional resources such as HMDB, BioCyc,
203 MetaNetX, ChEBI, and SEED. C) We collected
204 and retrieved kinetic parameters such as K_M , K_I ,
205 K_A , and K_{eq} constants from databases and D)
206 integrated them with synonyms associated with
207 each queried metabolite using compound identifier
208 mapping services. E) We integrated the resulting
209 parameters and assigned median values to the
210 model parameters. F) Next, we curated data from
211 studies reporting metabolite concentrations and
212 changes, and insulin secretion in pancreatic, islet,
213 and β -cell lines through a literature search. G)
214 Unit normalization was then performed to convert
215 reported metabolite concentrations and insulin
216 secretion to mmole/l (mM) and nmole/min/ml (β -
217 cell volume), respectively. H) Data normalization
218 was performed to remove systematic differences
219 between data reported in different studies and
220 experimental systems. I) Next, values for kinetic
221 parameters, initial concentrations, volumes, rate
222 equations, and annotations were integrated into

the stoichiometric model. J) We calibrated the 223
model by parameter optimization using time-course 224
and steady-state data and K) generated the final 225
SBML kinetic model using all the information. 226
L) Finally, we performed model predictions of 227
glycolytic intermediates and insulin response as a 228
function of varying glucose concentrations. Steps 229
were performed iteratively to fill gaps and extend 230
the data set and model. 231

2.3 Computational model 232

Using the established data set, we utilized 233
the aforementioned workflow to develop the first 234
consensus model of GSIS in the pancreatic β -cell. 235
The model is comprised of detailed glycolysis and 236
equations for insulin secretion which are coupled 237
to the cellular energy state (ATP/ADP ratio). The 238
metabolites and reactions incorporated into the 239
kinetic model are depicted in Fig. 3, and their 240
biochemical interactions are represented through 241
a system of ordinary differential equations. The 242
model consists of 21 enzyme-catalyzed reactions, 243
25 metabolites, and 91 parameters, and also includes 244
an empirical model that connects the energy state 245
of the β -cell to insulin secretion. 246

When glucose levels are high, GLUT transporter 247
allows glucose to enter the cell, and glucokinase 248
converts glucose to glucose-6-phosphate. The 249
upper glycolysis produces fructose-6-phosphate, 250
fructose-1,6-phosphate, and triose phosphates like 251
dihydroxyacetone phosphate and glyceraldehyde 252
phosphate. Lower glycolysis then leads to the 253
creation of 3-phosphoglycerate, 2-phosphoglycerate, 254
phosphoenolpyruvate, and pyruvate. Pyruvate can 255
be transformed into lactate or transported to the 256
mitochondria. For each glucose molecule, two ATP 257
molecules are produced. Changes in ATP/ADP ratio 258
trigger insulin secretion. 259

The SBML model is available 260
under a CC-BY4.0 license 261
from [https://github.com/matthiaskoenig/pancreas-](https://github.com/matthiaskoenig/pancreas-model) 262
[model](https://github.com/matthiaskoenig/pancreas-model). 263

264 2.4 Normalization of data

265 The aim of this study was to investigate
266 variations in glycolysis, glycolytic intermediates,
267 energy metabolites, and insulin secretion during
268 GSIS using the established model. In order to
269 integrate heterogeneous experimental data for each
270 metabolite and insulin secretion rate, we conducted
271 a two-step normalization process to standardize
272 time course and dose-response measurements. The
273 normalization process involved unit normalization
274 (as discussed in Sec. 4.7) and data normalization (as
275 discussed in Sec. 4.8) to normalize the diverse data
276 and eliminate systematic deviations for individual
277 studies. We present the case of glucose 6-phosphate
278 as an example of the normalization process (see
279 Fig. 4). The experimental curves were converted
280 to relative (fold) and unit-normalized absolute
281 measurements (Fig. 4A and Fig. 4B). To combine
282 the fold data and absolute data, we multiplied
283 the fold values by the basal concentration to
284 obtain absolute values (Fig. 4C). If the basal
285 metabolite concentration was not reported, we
286 used the mean curve of the absolute data at the
287 pre-incubation glucose dose of the experiment
288 to determine the basal value. For metabolites
289 consisting of only relative measurements, we used
290 the half-saturation K_m value of the metabolite as
291 an estimate for the basal concentration. Using
292 this strategy, we converted all fold-changes and
293 time courses to absolute data with standardized
294 units, which was then combined with the existing
295 absolute data. However, the standard deviation of
296 the combined data set measurements was high, and
297 large systematic differences between studies could
298 be observed. We determined scaling factors for
299 every study to minimize the difference between
300 all studies based on least-squares minimization (as
301 discussed in Sec. 4.8.1). The resulting normalized
302 data (Fig. 4D) was then used for model calibration.
303 We applied this procedure to all metabolites in the
304 model as well as the insulin secretion rate, reducing
305 the variability in the data substantially.

2.5 Changes in glycolytic metabolites and insulin secretion in GSIS 306 307

Our work has uncovered several key findings 308 related to GSIS. First, we found that almost all 309 glycolytic intermediates increase in a glucose- 310 dependent manner across a wide range of glucose 311 concentrations, as illustrated in Figures 5, 6, and 312 7. This increase in glycolytic intermediates is 313 accompanied by a corresponding increase in energy 314 metabolites, especially ATP and NADH. However, 315 one notable exception is ADP, which decreases 316 with increasing glucose levels. As a result, there 317 is a significant increase in ATP/ADP ratios in 318 β -cells with increasing glucose, a key factor in 319 insulin secretion. This phenomenon is robust across 320 different data sets, experimental systems, and 321 species. An important observation is that not only 322 ATP and NADH increase with increasing glucose, 323 but also the total ATP (ATP + ADP) and total 324 NADH (NAD + NADH). 325

Our model was able to predict the glucose- 326 dependent response of glycolytic intermediates 327 and insulin secretion with good agreement to 328 most experimental measurements, as summarized 329 in Table 1. We observed a dose-dependent 330 increase in glycolytic intermediates when glucose 331 concentrations were increased from 0.01 mM to 332 35 mM. The model predicts that steady states of 333 glycolytic metabolites under constant glucose are 334 reached after approximately 20 minutes, with only 5- 335 10 minutes required to reach steady state according 336 to our simulations. 337

Figure 8A illustrates the relationship between 338 glucose dose and insulin release, while Figure 8B 339 shows the effect of varying the ATP/ADP ratio 340 on the insulin response. Specifically, the ATP 341 and ADP concentrations of the β -cell increase and 342 decrease, respectively, with the external glucose 343 dose, resulting in an increased ATP/ADP ratio 344 that triggers insulin release. The model is able 345 to reproduce the steady-state insulin secretion 346 depending on glucose concentration, but fails to 347 describe the fast initial insulin release. 348

349 2.6 Sensitivity analysis of parameters 350 affecting GSIS

351 To determine how the model parameters affect
352 the rate of insulin release, we performed a local
353 sensitivity analysis (Sauro, 2020). Figure 8C shows
354 the sensitivity of insulin flux to a 10% change
355 in model parameter values at different glucose
356 concentrations. The rate of insulin secretion depends
357 on the ATP/ADP ratio, so perturbing parameters
358 that affect ATP formation and consumption has
359 strong effects. Figure 8D shows the highly sensitive
360 parameters that have positive and negative effects
361 on insulin secretion, including factors affecting
362 ATP consumption, ATP formation, hexokinase,
363 phosphofructokinase, and ATP/ADP-dependent
364 insulin secretion.

365 In conclusion, our systematic pathway modeling
366 workflow provides insights into the key mechanisms
367 of GSIS in the pancreatic β -cell.

3 DISCUSSION

368 We have developed a comprehensive kinetic
369 model of GSIS in the pancreatic β -cell that can
370 simulate glucose-dependent changes in glycolytic
371 intermediates, ATP/ADP ratio, and their effect
372 on insulin secretion. The main objective of this
373 study was to establish a standardized workflow for
374 data integration and normalization to construct a
375 tissue-specific model of glycolysis and GSIS in the
376 β -cell. Although we did not model other important
377 pathways related to ATP homeostasis, such as the
378 citric acid cycle, the pentose phosphate pathway,
379 and the respiratory chain, our workflow can be
380 easily extended to include them. Incorporating
381 these pathways into our model will enable us to
382 explicitly model the regulatory effect of downstream
383 metabolites on the ATP/ADP ratio and insulin
384 secretion. Previous studies have shown that fatty
385 acids and amino acids can also induce insulin
386 secretion in addition to glucose. Therefore, linking
387 glucose metabolism with fatty acid and amino
388 acid metabolism could help in understanding the
389 insulinotropic effects of other fuel sources.

The increase in ATP levels triggers a cascade 390
of events that culminate in the release of 391
insulin from β - cells. Precisely, high ATP levels 392
prompt the closure of ATP-sensitive potassium 393
channels (Ashcroft, 2006). Consequently, the 394
cell membrane depolarizes, opening voltage-gated 395
calcium channels, which allows calcium influx. The 396
influx of calcium triggers exocytosis of insulin- 397
containing vesicles, leading to the release of insulin 398
into the bloodstream (Rorsman and Braun, 2013; 399
Guerrero-Hernandez and Verkhratsky, 2014). These 400
electrophysiological changes resulting in insulin 401
secretion were not modeled explicitly, but the 402
effect of the ATP/ADP ratio on insulin secretion 403
was modeled using a phenomenological (Hill-type) 404
expression. Consequently, the model's predictive 405
capacity is limited to the steady-state glucose- 406
insulin secretion dynamics. Expanding the model 407
to explicitly describe these phenomena would 408
allow to study experimentally observed patterns 409
such as biphasic insulin secretion (Pedersen et al., 410
2008). Of note, the dynamics changing glycolytic 411
intermediates were correctly described by the 412
model. 413

Although our model has some limitations, it 414
represents the first data-driven approach to integrate 415
information from diverse sources and experimental 416
setups. Moreover, it provides the first systematic 417
analysis of the glycolytic changes that occur during 418
insulin secretion in response to different glucose 419
levels. Our study reveals that in GSIS, almost 420
all glycolytic intermediates increase in a glucose- 421
dependent manner as do total ATP and NADH, 422
which is a significant finding. 423

Our model was developed to address the 424
limitations of existing pancreatic β -cell models 425
of glucose-insulin kinetics. These models often 426
suffer from several drawbacks such as limited 427
evaluation to a single data set, non-standardized 428
formats of experimental data and kinetic parameters, 429
and non-reproducible formats. To overcome these 430
limitations, we have created open, free, and FAIR 431
assets that can be used for the study of pancreatic 432
physiology and GSIS. These assets include a fully 433
reproducible SBML model of pancreatic β -cell 434

435 glycolysis, a data curation workflow, strategies for
436 unit and data normalization, and a large database
437 of metabolic data of the pancreatic β -cell. Our
438 systematic model-building workflow can be used as
439 a blueprint to construct reproducible kinetic models
440 of cell metabolism.

441 Computational modeling faces a significant
442 challenge due to the substantial variation in data
443 across different experimental systems, species, and
444 cell lines. Often, relative data instead of absolute
445 data is reported, further complicating the task
446 of data integration. In this study, we developed
447 a reliable data normalization workflow that was
448 applied to experimental and clinical data from
449 39 studies conducted over the past 50 years on
450 pancreatic, islet, and β -cell function in various
451 species and cell lines. Our approach substantially
452 reduced data heterogeneity and revealed a highly
453 consistent response in glycolytic metabolites and
454 insulin secretion. The high degree of conservation
455 in the system of GSIS may have contributed to
456 the effectiveness of the normalization workflow, as
457 similar mechanisms are at play in different species,
458 and the general changes can be observed across
459 various experimental systems.

460 The study has laid a strong groundwork for
461 enhancing our comprehension of the underlying
462 reasons behind impaired insulin secretion. By
463 mapping proteomics or transcriptomics data onto
464 specific pathways, the developed model could be
465 utilized to gain further insight into changes in GSIS,
466 for instance in diabetic patients.

467 Furthermore, this model can serve as a crucial
468 component for physiological whole-body models
469 of glucose homeostasis, allowing researchers to
470 investigate the relationship between insulin release
471 and glucose uptake by insulin-responsive tissues.

472 In conclusion, this study utilized a systematic
473 modeling workflow to gain insight into the key
474 mechanisms involved in glucose-stimulated insulin
475 secretion (GSIS) in pancreatic β -cells. When
476 extended for translational purposes in clinical
477 settings, it can serve to create reference models to
478 identify variations in subjects which can lead to

useful inferences regarding underlying metabolic 479
conditions with therapeutic relevance. 480

4 METHODOLOGY

The workflow for building the kinetic model is 481
illustrated in Fig. 2, with the following sections 482
providing information on the individual steps. 483

4.1 Stoichiometric model 484

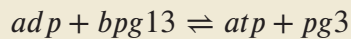
Chemical formulas and charges were assigned 485
to all metabolites, and reactions were examined 486
to ensure that they maintained mass and charge 487
balance. The kinetic model encompasses glycolytic 488
reactions and correlates the energy status of the β - 489
cell with insulin secretion. sbmlutils (König, 2022c) 490
was used to create and validate the model, while 491
cy3sbml (König et al., 2012b) was used to confirm 492
its coherence. The mass and charge balance of the 493
system was verified using cobrapy (Ebrahim et al., 494
2023). 495

4.2 Metadata integration 496

Adding semantic annotations to models 497
is an essential aspect of improving their 498
interoperability and reusability, as well as 499
facilitating data integration for model validation 500
and parameterization (Neal et al., 2019, 2020). 501
To describe the biological and computational 502
significance of models and data in a machine- 503
readable format, semantic annotations are encoded 504
as links to knowledge resource terms. Open 505
modeling and exchange (OMEX) metadata 506
specifications were employed to annotate model 507
compartments, species, and reactions with metadata 508
information (Fig. 2B). 509

Case study: Phosphoglycerate kinase

The enzyme phosphoglycerate kinase (PGK) catalyses the conversion of 1,3-biphosphoglycerate (*bpg13*) and ADP to form 3-phosphoglycerate (*pg3*) and ATP.



In our model, PGK is described by the following annotations:

SBO:0000176, vmhreaction/PGK,
bigg.reaction/PGK,
kegg.reaction/R01512, ec-code/2.7.2.3,
biocyc/META:PHOSGLYPHOS-RXN,
uniprot:P00558, uniprot:P07205.

510

511 The model components, including physical
512 volumes, reactions, metabolites, and kinetic-rate
513 laws, were annotated using Systems Biology
514 Ontology (SBO) terms, which describe the
515 computational or biological meaning of the model
516 and data (Courtot et al., 2011). Biomedical
517 ontology services such as Ontology Lookup Service
518 (OLS) (Cote et al., 2010), VMH (Noronha et al.,
519 2019), and BiGG (King et al., 2016) were used
520 to collect these terms. Additional information for
521 species and reactions were gathered from various
522 databases such as HMDB, BioCyc, MetaNetX,
523 ChEBI, and SEED. For instance, the model's
524 metabolites were annotated with identifiers from
525 VMH, BiGG, KEGG, HMDB, BioCyc, ChEBI,
526 MetaNetX, and SEED, while reactions were
527 annotated with VMH, Rhea, MetaNetX, SEED,
528 BiGG, BioCyc, and KEGG identifiers (Hari and
529 Lobo, 2022). Enzymes catalyzing reactions were
530 annotated with identifiers from enzyme commission
531 (EC) numbers, UniProt (The UniProt Consortium,
532 2017), and KEGG. Finally, the annotations
533 were incorporated into the SBML file using
534 sbmlutils (König, 2022c) and pymetadata (König,
535 2022b).

Case study: 1,3-biphosphoglycerate

There is currently a bottleneck in data integration due to the use of multiple synonyms to refer to a single compound in data repositories. For instance, *bpg13* is identified by different names in SABIO-RK (*Glycerate 1,3-bisphosphate, 3-phospho-D-glyceroyl phosphate*) and BRENDA (*3-phospho-D-glyceroyl phosphate*). Additionally, the labeling of *1,3-biphosphoglycerate*, abbreviated as *DPG*, varies across existing β -cell models (e.g., *1,3-bisphospho-D-glycerate* in (Jiang et al., 2007) and *1,3-biphosphoglycerate* in (Salvucci et al., 2013)). Overall, *bpg13* is associated with seven synonyms: *1,3-Bisphospho-D-glycerate*, *13dpg*, *3-Phospho-D-glyceroylphosphate*, *Glycerate 1,3-bisphosphate*, *3-phospho-d-glyceroyl-phosphate*, *1,3-diphosphoglyceric acid*, *3-Phospho-D-glyceroyl phosphate*. This issue makes it difficult to integrate data and information from different resources, highlighting the need to link chemical entities in the model to knowledge resource terms.

In our model, *bpg13* is clearly described by the following metadata annotations: SBO:0000247, vmhmetabolite/13dpg, bigg.metabolite/13dpg, kegg.compound/C00236, biocyc/META:DPG, CHEBI:16001, inchikey:LJQLQCAXBUHEAZ-UWTATZPHSA-N.

The formula and charge of *bpg13* are $C_3H_4O_{10}P_2$ and -4, respectively.

536

4.3 Kinetic parameters

537

Kinetic parameters, such as half-saturation
538 constants (K_M), inhibition constants (K_I),
539 activation constants (K_A), and equilibrium
540 constants (K_{eq}), were gathered from literature
541 and a variety of databases (see Fig. 2C).
542 Values were programmatically accessed
543

544 from UniProt (The UniProt Consortium,
545 2017), BRENDA (Placzek et al., 2017) using
546 brendapy (König, 2022a), and SABIO-RK (Wittig
547 et al., 2018). These databases were searched
548 using an organism's NCBI taxonomy identifier
549 and reaction EC number as input search terms.
550 Various parameters, including measurement type
551 (K_m , K_i , and K_a), experimental conditions (pH,
552 temperature), KEGG reaction identifiers, enzyme
553 type (wildtype or mutant), associated metabolite
554 identifiers (SABIO compound name or BRENDA
555 ligand id), UNIPROT identifiers associated with the
556 isoforms of an enzyme, source tissue, and details
557 of data source (PubMed identifier) were obtained.
558 Since there is limited availability of kinetic data
559 for *Homo sapiens*, we also searched for parameter
560 values reported in studies of animal species that are
561 closely related to humans and utilized them if no
562 data were available for humans.

563 4.4 Synonym mapping

564 To map compound synonyms associated with
565 each queried metabolite, we utilized compound
566 identifier mapping services and available metadata
567 annotations. First, we associated the name of each
568 compound with internal database identifiers, such
569 as the internal identifier of Glycerone-phosphate in
570 SABIO, which is 28. Then, we linked the internal
571 identifiers to external identifiers, such as those
572 from ChEBI and KEGG. The external identifiers
573 associated with the SABIO ligand identifier were
574 obtained from cross-ontology mappings available
575 in SABIO-RK. Similarly, we queried the REST
576 API of UniChem to obtain the external identifiers
577 associated with the BRENDA ligand identifier. By
578 doing so, we were able to map most of the kinetic
579 parameters to their respective compounds (Fig. 2D).

580 4.5 Model parameters

581 For each parameter in the model, the median
582 value was calculated after synonym mapping
583 and the values were assigned to the model
584 parameters, see Fig. 2E. This was performed for
585 initial concentrations, equilibrium K_{eq} constants,

half-saturation constants K_m , inhibition K_i , and 586
activation K_a constants. 587

4.6 Data curation 588

The next step involved curating data from 589
studies that reported metabolite values, insulin 590
secretion, or maximal velocities of glycolytic 591
reactions V_{max} in pancreatic, islet, and β -cell 592
lines (Fig. 2F). Relevant studies were identified 593
through a literature search in PubMed, with a 594
focus on time course and dose-response profiles 595
of metabolite concentrations for metabolites 596
and insulin secretion. Tissue homogenates were 597
prepared by isolating islets from rodents, humans, or 598
insulin-secreting cell lines (see Tab. 1). Assays were 599
performed by stimulating the medium with various 600
pre-incubation and incubation concentrations of 601
glucose. To curate the data, established curation 602
workflows from PK-DB (Grzegorzewski et al., 603
2021b), which were applied in a recent meta- 604
analysis (Grzegorzewski et al., 2021a), were used. 605
The numerical data was digitized by extracting 606
the data points from the figures and tables using 607
WebPlotDigitizer (Rohatgi, 2021). The incubation 608
time and glucose concentration of the stimulation 609
medium were recorded for all measurements, and 610
meta-information such as organism and tissue type 611
were documented. 612

The data is available under a CC-BY 4.0 license 613
from [https://github.com/matthiaskoenig/pancreas-](https://github.com/matthiaskoenig/pancreas-model) 614
[model](https://github.com/matthiaskoenig/pancreas-model). In this study, version 0.9.5 of the data set is 615
used (Deepa Maheshvare and König, 2023). 616

4.7 Unit normalization 617

The data measured in different studies is 618
often reported in different units. Therefore, unit 619
normalization was performed to integrate the data 620
and convert metabolite concentrations and insulin 621
secretion to standardized units of mmole/l (mM) 622
and nmole/min/ml (β -cell volume), respectively 623
(Fig. 2G). 624

Absolute measurements reported in metabolic 625
profiling studies were found in various units such 626
as per gram DNA, per gram wet weight or dry 627

628 weight of the islet tissue, per cell, per islet, 629 etc. To use these values for model calibration, 630 both the absolute and relative measurements were 631 first converted to concentration units in mM. The 632 absolute values were converted to model units 633 by multiplying the raw values with appropriate 634 unit conversion factors. For instance, the islet 635 content of glucose 6-phosphate, G6P, (pmol/islet) 636 was converted to concentration units (mM) using 637 the distribution volume of water in the islet 638 (2nl/islet) (Ashcroft et al., 1970) as the conversion 639 factor. Relative measurements were mainly reported 640 with reference to a basal concentration. These 641 relative measurements were converted to absolute 642 quantity by multiplying the fold values with the 643 respective metabolite concentration at the basal or 644 pre-incubation concentration of glucose.

645 4.8 Data normalization and integration

646 Data collected from experiments performed in 647 different laboratories, under different experimental 648 conditions, and with different animal species 649 showed significant variability after unit 650 normalization. Therefore, data normalization was 651 performed to eliminate systematic discrepancies 652 between data reported in different studies (as 653 shown in Fig. 2H). To achieve this, least squares 654 optimization was used to minimize the distance 655 between individual experimental curves and 656 the weighted average of all curves for a given 657 metabolite. The data normalization process involved 658 a two-step procedure in which the steady-state 659 data were first normalized for each metabolite. 660 The resulting steady-state normalization was then 661 used to normalize the time course data for that 662 metabolite (see Fig. 4 for the example of glucose-6 663 phosphate).

664 4.8.1 Steady-state data normalization

665 Steady-state (ss) experiments consisted of pre- 666 incubation with one glucose dose followed 667 by incubation with another glucose dose. 668 The steady state data of the experiment α , 669 $(c_0^\alpha, c_1^\alpha, \dots, c_n^\alpha)$ observed at n incubation glucose 670 doses $(d_0^\alpha, d_1^\alpha, \dots, d_n^\alpha)$ is expressed by the piecewise

linear-interpolation function C^{ss} . Here, α belongs 671 to the set of steady-state experiments $1 \leq \alpha^{ss}$ with 672 $N^{\alpha^{ss}}$ being the number of steady-state experimental 673 curves of the metabolite s . 674

Mean curve. The mean steady-state curve $\overline{C^{ss}}$ 675 of each metabolite s is calculated as the weighted 676 average of all experimental curves. The data points 677 of the mean curve were interpolated using a 678 piecewise smooth spline function. For data sets 679 consisting of 2 data points, a linear interpolation 680 was used. 681

We formulate a least-squares optimization 682 problem to minimize the distance between the 683 individual experimental curves and the mean 684 curve $\overline{C^{ss}}$. The cost function \mathbf{F} of the optimization 685 problem is given by, 686

$$F(f^\alpha) = \sum_{i=1}^n (f^\alpha \cdot C^{ss}(d_i^\alpha) - \overline{C^{ss}}(d_i^\alpha))^2 \quad (1)$$

In Eq. 1, $C^{ss}(d_i^\alpha)$ and $\overline{C^{ss}}(d_i^\alpha)$ are the function 687 values of the individual and mean interpolation 688 function at the i^{th} value of the glucose dose. N is 689 the number of glucose values in the dose-response 690 curve of the experiment α . 691

For each experimental curve, the factor f^α was 692 determined so that the residual error in Eq. 1 is 693 minimized. The residual error is minimum at the 694 point where the derivative of the cost function \mathbf{F} 695 is zero. Taking the partial derivative of Eq. 1 with 696 respect to the scale transformation parameter gives 697 factor f^α of the experimental curve α (Eq. 2). 698

$$f^\alpha = \frac{\sum C^{ss}(d_i^\alpha) \overline{C^{ss}}(d_i^\alpha)}{\sum (C^{ss}(d_i^\alpha))^2} \quad (2)$$

The scale factors of all steady state curves 699 $(f^1, \dots, f^{N^{\alpha^{ss}}})$ were determined by minimizing 700 the respective cost functions $(F(f^1), \dots, F(f^{N^{\alpha^{ss}}}))$. 701 Multiplying the experimental curve C^α by the 702 scaling factor f^α shifts the experimental curve 703 towards the mean curve. A new mean curve can 704

705 be calculated with the scaled data. The curves were
706 scaled iteratively until all f^α converged.

707 4.8.2 Time course data normalization

708 Time course (tc) experiments consisted of pre-
709 incubation with one glucose dose followed by
710 incubation with another glucose dose. The time-
711 dependent data of the time course experiment
712 β ($c_0^\beta, c_1^\beta, \dots, c_m^\beta$) observed at m time points
713 ($t_0^\beta, t_1^\beta, \dots, t_m^\beta$) is expressed by the piecewise linear-
714 interpolation function C^β . Here, β belongs to the
715 set of time course experiments $1 \leq \beta \leq N^{\beta_{tc}}$ with
716 $N^{\beta_{tc}}$ being the number of time course experimental
717 curves of the metabolite s . For normalization, each
718 time course was scaled by a factor f^β .

719 For a given incubation glucose dose d^β , the
720 metabolite concentration at the last time point
721 $C^{tc}(t_m)$ corresponds to the steady state value reached
722 for the given d^β

$$f^\beta \cdot C^{tc}(t_m) - \overline{C^{ss}}(d^\beta) = 0 \quad (3)$$

723 The scaling factor for the time course experiment
724 follows as

$$f^\beta = \frac{\overline{C^{ss}}(d^\beta)}{C^{tc}(t_m)} \quad (4)$$

725 4.9 Model inputs

726 The SBML model was generated by specifying
727 initial concentrations, rate expressions, parameter
728 values, and compartmental volumes as the model
729 inputs, see Fig. 2I.

730 *Volume.* The physical volume of the cytoplasmic
731 compartment and the β -cell volume were obtained
732 from the values reported in a morphometric study
733 of β -cells (Dean, 1973).

734 *Initial concentrations.* The initial concentrations
735 of glycolytic intermediates were obtained from
736 the mean curve $\overline{C^{ss}}$ (Sec. 2.1) at a basal glucose
737 concentration of 3 mM. The initial value of glucose
738 in the external/blood compartment is 3 mM.

The initial concentrations of cofactors were 739
expressed as polynomial functions passing through 740
the data points of the mean curve, which is computed 741
as the weighted average of data normalized 742
experimental curves (Sec. 2.1). In the SBML model, 743
the polynomial expressions were defined using 744
assignment rules. 745

Kinetic constants. The median values of the 746
half-saturation or Michaelis-Menten constants K_m 747
(Sec. 4.5), were assigned to the model parameters. 748

Equilibrium constants. The values of the 749
equilibrium constants K_{eq} were collected 750
from NIST (Goldberg and Tewari, 2003) and 751
EQUILIBRATOR (Noor et al., 2013). 752

Model equations. For all the glycolytic reactions, 753
the biochemical interactions were expressed using 754
modular rate laws (Liebermeister et al., 2010) of the 755
form Eq. 5. 756

$$v = \frac{V_{max} \prod_i a_i \left(1 - \frac{\Gamma}{K_{eq}}\right)}{\prod_i (1 + a_i) + \prod_j (1 + b_j) - 1} \quad (5)$$

Here, a_i is S_i/Km_s , b_i is P_i/Km_p , S refers to 757
the substrate and P refers to the product. K_{eq} is 758
the equilibrium constant and Γ is the mass-action 759
ratio (Liebermeister et al., 2010). 760

The use of detailed mechanistic rate laws was 761
avoided due to the challenges associated with 762
finding a large number of parameter values. 763

Insulin secretion was modeled via a 764
phenomenological equation depending on 765
ATP/ADP ratio. The insulin release flux given 766
by Eq. 6, is characterized by three parameters, 767
the maximal rate of insulin release V_{max} , the Hill 768
coefficient n , and K_m the ratio of ATP/ADP that 769
results in half-maximal insulin release. 770

$$v^{IRS} = V_{max}^{IRS} \frac{\left(\frac{ATP}{ADP}\right)^n}{\left(K_m\right)^n + \left(\frac{ATP}{ADP}\right)^n} \quad (6)$$

771 *Boundary metabolites and reactions.* Species
772 in the external and mitochondrial compartments
773 were assumed to be boundary species with
774 constant concentrations, i.e. glucose and lactate
775 in the external compartment and pyruvate in the
776 mitochondrial compartment were held constant.
777 Some boundary reactions were modeled as
778 irreversible reactions, i.e. the export of lactate and
779 the transport of pyruvate in the mitochondrion.

780 *Metabolites determined by rate rules.* To account
781 for glucose-dependent changes in the concentrations
782 of phosphate, NAD, and NADH, polynomial
783 functions were used to express the concentrations
784 as rate rules. This approach ensured that the
785 concentration of fixed metabolites in the system
786 increased as a function of glucose dose.

787 *Changes in total adenine nucleotides.* The sum
788 of adenine nucleotides ($ATP + ADP = ATP_{tot}$)
789 changes with glucose. To account for these changes,
790 a reaction ΔATP was added that changes the total
791 ATP according to the observed steady-state data for
792 a given glucose value (Eq. 7).

$$\Delta ATP = f(ATP_{tot}(glc) - (ATP + ADP)) \quad (7)$$

793 The $ATP_{tot}(glc)$ values are determined by the
794 interpolating polynomial of the mean steady-state
795 glucose dose response of the ATP+ADP data.

796 4.10 Model calibration

797 The normalized time-course and steady-state data was
798 used for model calibration and parameter estimation
799 (Fig. 2J). An overview of the subset of data used for
800 model calibration is shown in Fig. 1. The following
801 data were not used: NADH and NAD were fixed
802 metabolites in the model, with NAD/NADH and
803 NADH+NAD calculated from the metabolites. Total
804 ATP was calculated by summing ATP and ADP, and
805 ATP ratio was calculated by finding the ratio. The insulin
806 secretion rate (IRS) was used to derive the parameters
807 of the IRS function.

808 A subset of the V_{max} parameters was optimized to
809 minimize the error between model predictions and

experimental observations. The cost function is given by 810
the sum of squares of residuals 811

$$F(\mathbf{P}) = \sum_{\alpha,s} (\mathbf{c}_s^\alpha - \mathbf{c}_s^{\mathcal{M}}(\mathbf{P}))^2 \quad (8)$$

In Eq. 8, \mathbf{c}_s^α is the concentration of the metabolite 812
 s in the experiment α and $\mathbf{c}_s^{\mathcal{M}}$ is the concentration 813
of the metabolite s predicted by the model \mathcal{M} . \mathbf{P} 814
is the set of 16 parameters of maximum reaction 815
rates V_{max} . The experimental data of all transient 816
metabolites in the model were stored in spreadsheets. 817
The parameter estimation simulation experiments were 818
set up using basiCO (Bergmann, 2023), the Python 819
interface of COPASI (Hoops et al., 2006). The incubation 820
glucose concentration and incubation time were mapped 821
to the independent variable (glc_{ext} , glucose in the 822
external compartment) and model time, respectively. 823
The transient metabolites were assigned to the model 824
elements as dependent variables. The mean values of 825
 V_{max} calculated from the curated values of the enzyme 826
activities were assigned as initial values. The lower 827
and upper bounds specified for the reaction rates V_{max} 828
were set to 0 and 10000, respectively. The calculations 829
were performed using Cloud-COPASI, the front-end to 830
a computer cluster at the Centre for Cell Analysis and 831
Modelling. Cloud-COPASI is an extension of Condor- 832
COPASI (Kent et al., 2012). 400 iterations of parameter 833
estimation were performed on Cloud-COPASI using the 834
SRES algorithm, a global optimization method. The 835
optimal values of the parameter set were obtained from 836
the iteration that yielded the minimum objective value 837
and updated in the model. 838

4.11 Kinetic model and model predictions 839

All information was written into the model, validation 840
was performed using sbmlutils, and model simulations 841
were performed, see Fig. 2K, L. 842

Finally, we performed model predictions of 843
glycolytic intermediates and insulin response as a 844
function of varying glucose concentrations. The set of 845
differential equations was numerically integrated using 846
basiCO (Bergmann, 2023) based on COPASI (Hoops 847
et al., 2006) and sbmlsim (König, 2021) based on 848
libroadrunner (Welsh et al., 2023; Somogyi et al., 849

850 2015). For the glucose dose-response, glucose was
851 varied as `linspace(0.01, 35, num=11)` and
852 the model was simulated to steady-state. For the time
853 course simulations, glucose was varied identically and
854 simulations were run for 60 min. Simulations were
855 performed either with COPASI or independently using
856 libroadrunner to ensure reproducibility of key model
857 results.

858 The model is available in SBML (Hucka et al.,
859 2019; Keating et al., 2020) under a CC-BY 4.0 license
860 from [https://github.com/matthiaskoenig/pancreas-](https://github.com/matthiaskoenig/pancreas-model)
861 [model](https://github.com/matthiaskoenig/pancreas-model). In this study, version 0.9.5 of the model is
862 presented (Deepa Maheshvare and König, 2023).

CONFLICT OF INTEREST STATEMENT

863 The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

864 DM, SR, MK, and DP conceived and designed the
865 study. DM and MK developed and implemented the
866 computational model and data normalization workflow,
867 and performed the analysis. DM curated the experimental
868 data, performed parameter estimation, and drafted
869 the initial version of the manuscript. All authors
870 read, discussed the results, revised, and approved the
871 manuscript.

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Table 1. Overview of studies reporting concentrations of metabolites used for model calibration.

Study	PMID	Metabolites	Species	Measurement	Steady-state	Time course	Citation
Akhtar1977	19330	G6P	Wistar rats	Absolute	✓		Akhtar et al. (1977)
Alcazar2019	31632354	IRS	Human, C57BL6/J mice	Absolute	✓	✓	Alcazar and Buchwald (2019)
Ammon1979	36318	NAD, NADH/NAD, NADH+NAD, NADH	Wistar rats	Absolute	✓	✓	Ammon et al. (1979)
Ammon1998	9582515	NAD, ATP/ADP, NADH, NADH+NAD, IRS, NADH/NAD	Wistar rats	Absolute	✓		Ammon et al. (1998)
Ashcroft1970	4919469	G6P	Albino mice	Absolute	✓		Ashcroft et al. (1970)
Ashcroft1973	4148924	ATP, IRS	White mice	Absolute	✓	✓	Ashcroft et al. (1973a)
Ashcroft1973b	4199014	G6P	Theillers original strain mice, Wistar rats	Absolute	✓	✓	Ashcroft et al. (1973b)
Ashcroft1979	44196	PYR	Wistar rats	Absolute	✓		Ashcroft and Christie (1979)
Brun1996	8549864	IRS	HIT-T15 β -cell line	Absolute	✓	✓	Brun et al. (1996)
Corkey1989	2689441	IRS	HIT β -cell line	Absolute	✓		Corkey et al. (1989)
Detimary1996	8702800	ATP, ADP, ATP+ADP, ATP/ADP, IRS	NMRI mice	Absolute	✓	✓	Detimary et al. (1996)
Detimary1998	9852040	ATP, ADP, ATP+ADP, ATP/ADP	Wistar rats	Absolute	✓		Detimary et al. (1998)
Ewart1983	6313455	PEP, IRS	Sprague-Dawley rats	Absolute	✓		Ewart et al. (1983)
Giroix1984	6388570	PEP, IRS	Albino rats	Absolute	✓		Giroix et al. (1984)
Guay2013	24130841	DHAP, ATP, PYR, LAC, NADH/NAD, IRS	INS 832/13 β -cell line	Relative	✓		Guay et al. (2013)
Hedeskov1987	3551925	PYR, LAC, NADH/NAD, IRS	Theillers original strain mice	Absolute	✓		Hedeskov et al. (1987)
Huang2014	24564396	G6P, DHAP, PG3, PYR, LAC	INS 832/13 β -cell line	Absolute	✓	✓	Huang and Joseph (2014)
Johnson2007	17360975	IRS	Human, Sprague-Dawley rats, C57BL6 mice, MIN6 β -cell line	Absolute	✓		Johnson et al. (2007)
Lamontagne2009	19406947	APT, IRS	INS 832/13 β -cell line	Relative	✓		Lamontagne et al. (2009)
Liu1998	9576750	G6P, IRS	Sprague-Dawley rats	Absolute	✓		Liu et al. (1998)
Liu2004	14660628	G6P, PYR, IRS	Sprague-Dawley rats	Absolute	✓		Liu et al. (2004)
Malaisse1977	27353	ATP, ADP, ATP+ADP, ATP/ADP, NAD, NADH, NADH+NAD, NADH/NAD	Albino rats	Absolute	✓		Malaisse et al. (1978)
Malaisse1987	2434137	ATP, ADP, ATP+ADP, ATP/ADP	Albino rats	Absolute	✓		Malaisse and Sener (1987)
Malinowski2020	32963286	PYR, LAC	INS-1 β -cell line	Relative	✓		Malinowski et al. (2020)
Malmgren2013	23476019	GLC, G6P, DHAP, PG3, PYR, LAC	INS-1 832/13 β -cell line	Relative	✓		Malmgren et al. (2013)
Matschinsky1961	4870741	GLC, G6P, FBP, ATP	Mice	Absolute	✓		Matschinsky and Ellerman (1968)
Matschinsky1976	136453	GLC, ATP	Sprague-Dawley rats	Absolute	✓		Matschinsky et al. (1976)
Meglason1986	2943567	F26P	Rats	Absolute	✓		Meglason and Matschinsky (1986)
Miwa2000	10919261	G6P, F6P, FBP, GRAP, DHAP	Wistar rats	Absolute	✓		Meglason et al. (1989)
Sener1978	29912	NAD, NADH, NADH+NAD	Albino rats	Absolute	✓		Sener et al. (1978)
Sener1984	6383351	F26BP	Albino rats	Absolute	✓	✓	Sener et al. (1984)
Spegel2013	23282133	PG2, PG3, PEP, PYR, LAC	INS-1 832/13 β -cell line	Relative	✓	✓	Spégel et al. (2013)
Spegel2015	25774549	G6P, ATP, PG2, PG3, PEP, PYR, LAC, IRS	INS-1 832/13 β -cell line	Relative	✓	✓	Spégel et al. (2015)
Sugden1977	332570	PEP	Albino Wistar rats	Absolute	✓		Sugden and Ashcroft (1977)
Taniguchi2000	10731696	G6P, F6P, FBP, GRAP, DHAP, ATP	Wistar rats	Absolute	✓	✓	Taniguchi et al. (2000)
Trus1979	220227	G6P, NADH, PHOS, IRS	Rats	Absolute	✓	✓	Trus et al. (1979)
Trus1980	6991311	G6P, ATP, ADP, ATP+ADP, NADH, PHOS, IRS	Holtzman rats	Absolute	✓	✓	Trus et al. (1980)
Xu2008a	18769905	IRS	Sprague-Dawley rats	Absolute	✓		Xu et al. (2008a)
Xu2008b	18802677	IRS	C57BL/6 mice, Sprague-Dawley rats, MIN-6 β -cell line	Absolute	✓		Xu et al. (2008b)

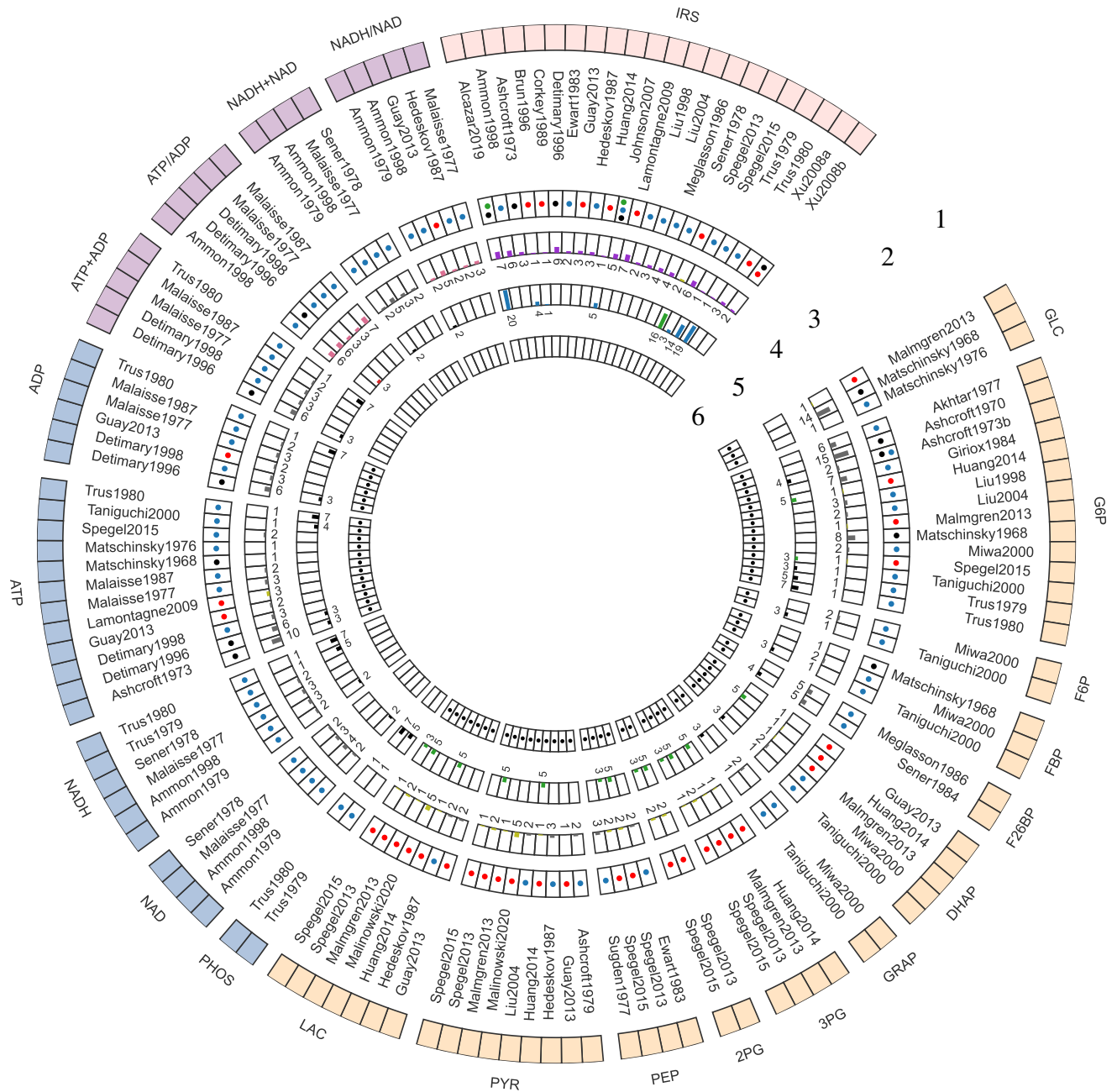


Figure 1. Curated data for model development and evaluation. The data description is detailed from the periphery to the center of the Circos plot. *1. Model elements:* The outermost layer provides an overview of the metabolites included in the data set. GLC: glucose, G6P: glucose 6-phosphate, F6P: fructose 6-phosphate, FBP: fructose 1,6-bisphosphate, F26BP: fructose 2,6-bisphosphate, DHAP: dihydroxyacetone phosphate, GRAP: glyceraldehyde 3-phosphate, BPG: 1,3-bisphosphoglycerate, 3PG: 3-phosphoglycerate, 2PG: 2-phosphoglycerate, PEP: phosphoenolpyruvate, PYR: pyruvate, LAC: lactate, PHOS: phosphate, NAD: nicotinamide adenine dinucleotide, NADH: reduced nicotinamide adenine dinucleotide, NADH total: NADH + NAD; NADH ratio: NADH/NAD; ATP: adenosine triphosphate, ADP: adenosine diphosphate, ATP total: ATP + ADP, ATP ratio: ATP/ADP, IRS: insulin secretion rate. The metabolites were grouped in the following categories: Color code: ● glycolytic intermediates, ● cofactors, ● cofactor ratio or sum, ● insulin secretion rate (IRS); *2. Studies:* The second layer depicts the islet-cell specific metabolite profiling studies curated from the literature; *3. Animal species:* The third layer indicates the animal species or cell line from which the data was curated. Color code: ● Rat, ● Human, ● Mouse, and ● Cell line data; *4. time course data:* The fourth layer shows a bar graph illustrating the number of data points collected from studies reporting time course data of metabolites. Color code: ● relative (or fold), ● concentration, ● ratio, ● rate measurements; *5. Steady-state data:* The fifth layer indicates the number of data points collected from studies reporting steady-state/ dose-response data of metabolites. Color code: ● relative (or fold), ● concentration, ● ratio, ● rate measurements; *6. Data used for parameter estimation:* The innermost layer indicates the subset of data used for parameter fitting.

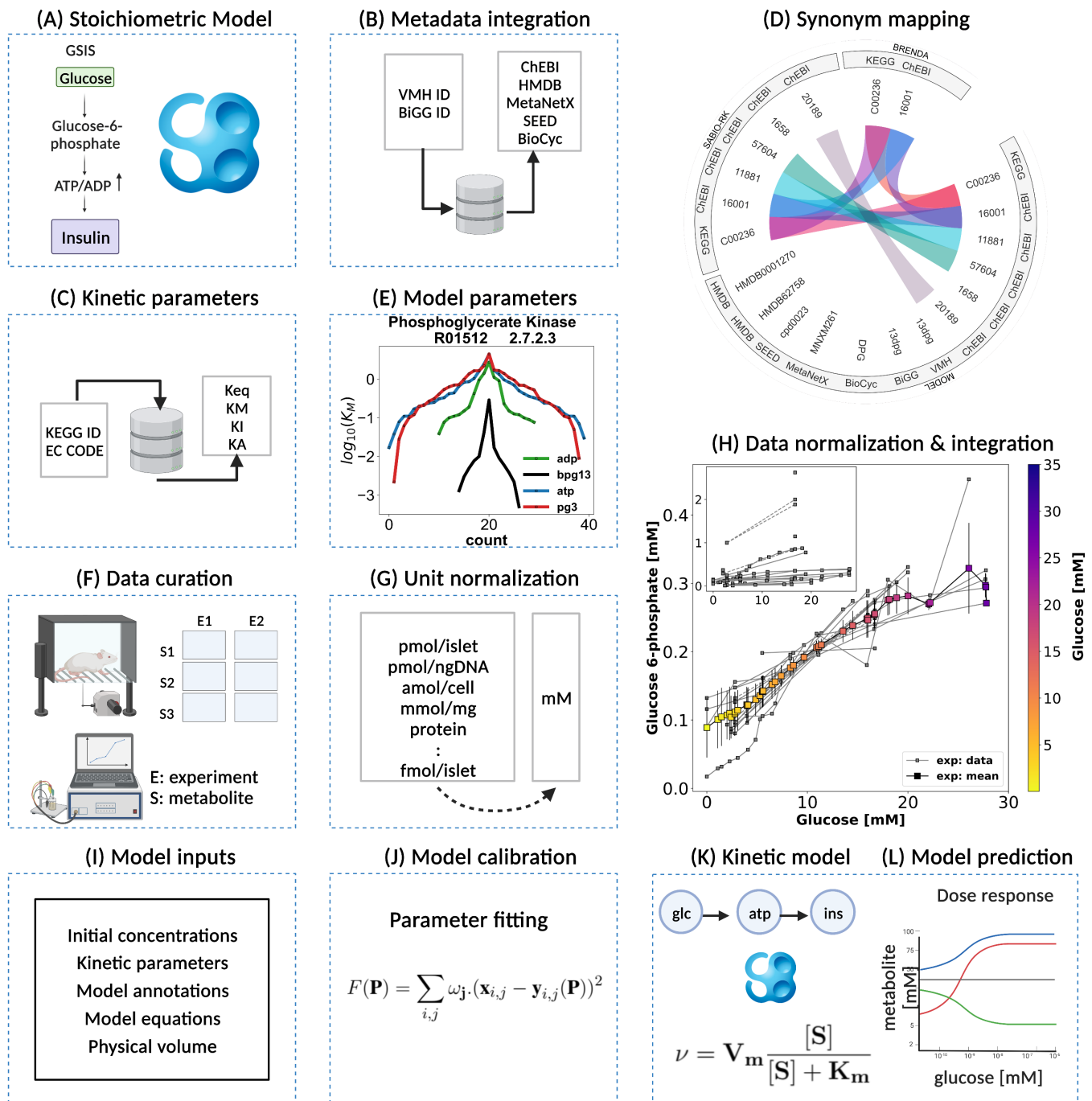


Figure 2. Kinetic model development workflow. (A) *Initial stoichiometric model in SBML.* Glycolytic reactions were collected from VMH database and existing models of glycolysis. (B) *Metadata integration.* VMH and BiGG database field identifiers were used to retrieve additional metadata such as HMDB, BioCyc, MetaNetX, ChEBI, and SEED database field identifiers. (C) *Synonym mapping.* The synonyms associated with each metabolite were queried using compound identifier mapping services. (D) *Kinetic parameters.* EC number and KEGG reaction identifiers were used to query half-saturation/Michaelis-Menten K_M , inhibition K_I , activation K_A , and equilibrium K_{eq} constants (synonym mapping was applied for all compounds). (E) *Model parameters.* The parameter values retrieved from different databases were merged and median values were assigned to the model parameters; (F) *Data curation.* A systematic literature search was performed and metabolite concentrations from islet cell studies were curated. (G) *Unit normalization.* Absolute and relative quantification of metabolite concentrations reported in heterogeneous units were converted to mM. (H) *Data normalization.* Systematic bias observed in the unit-normalized data was removed by performing least-squares minimization to minimize the distance between the mean curve of the unit-normalized data curves and the experimental curves of the unit-normalized data. (I) *Model inputs.* Values of kinetic parameters, initial concentrations, volumes, equations, and annotations have been assigned to the model entities. (J) *Model calibration.* Time course and steady-state data were used for parameter estimation. (K) *Kinetic SBML model.* The final kinetic SBML model was generated. (L) *Model prediction.* Glycolytic intermediates and insulin response were predicted as a function of varying glucose concentrations. Created with BioRender.com.

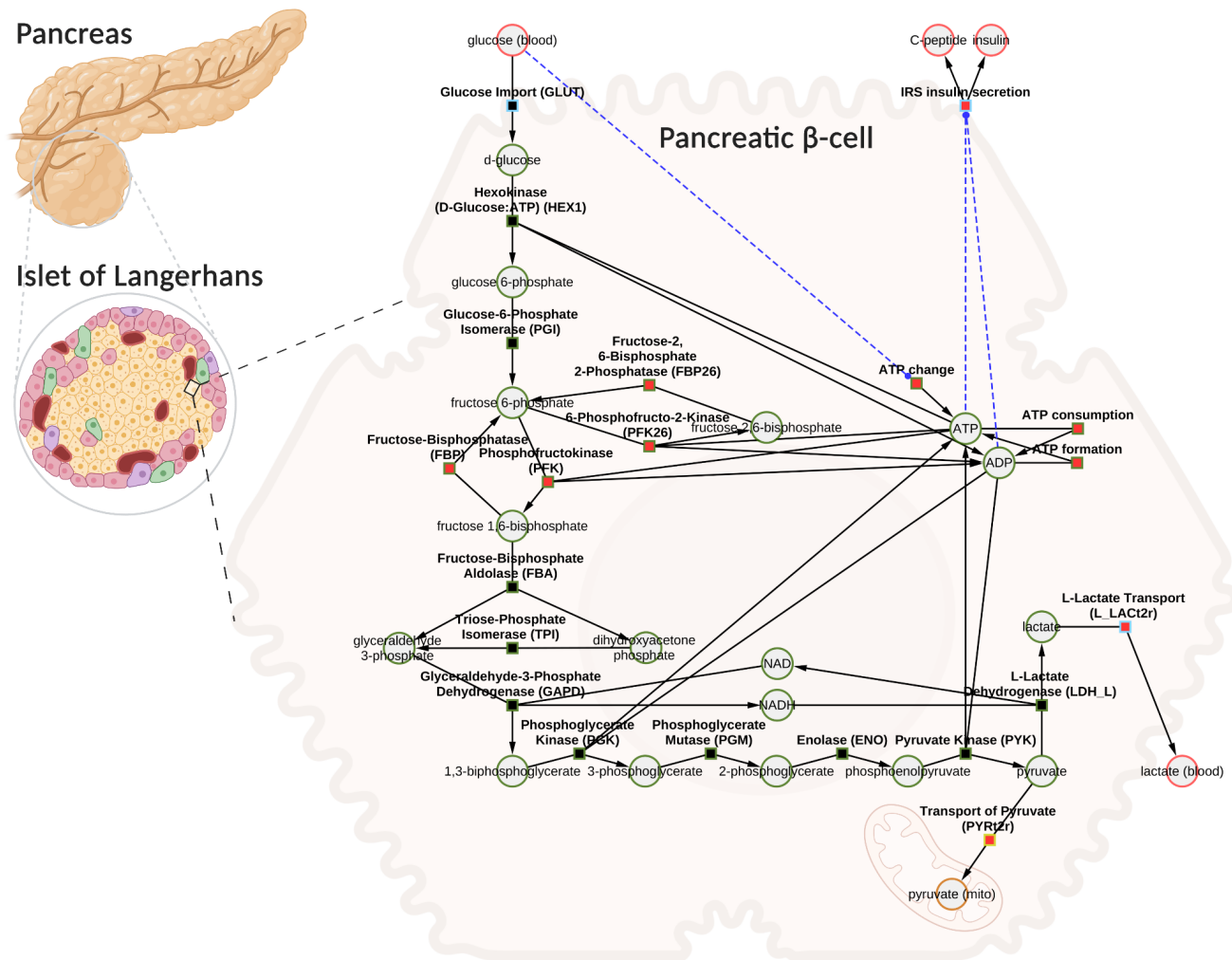


Figure 3. Computational model of glucose-stimulated insulin secretion (GSIS) in the pancreatic β -cell. The model consists of glycolysis and insulin secretion coupled to the energy state (ATP/ADP ratio). The GLUT transporter facilitates the uptake of glucose from the plasma into the cell. Glucose undergoes phosphorylation and the subsequent reactions lead to the production of pyruvate. Pyruvate can either be converted to lactate and exported into blood or transported to the mitochondria where it serves as a fuel source for the production of tricarboxylic acid cycle (TCA) intermediates (the TCA cycle has not been modeled). Depending on the external glucose concentrations, glycolysis intermediates and energy metabolites such as ATP, ADP, NAD, and NADH change. An increase in the ATP/ADP ratio as a result of changes in glucose triggers the cascade of signaling mechanisms that promote insulin secretion by the pancreatic β -cell. Phosphate, water, and hydrogen ions have been omitted from the diagram for clarity (but are included in the model for mass and charge balance). The network diagram was created using CysBML (König et al., 2012b). Created with BioRender.com.

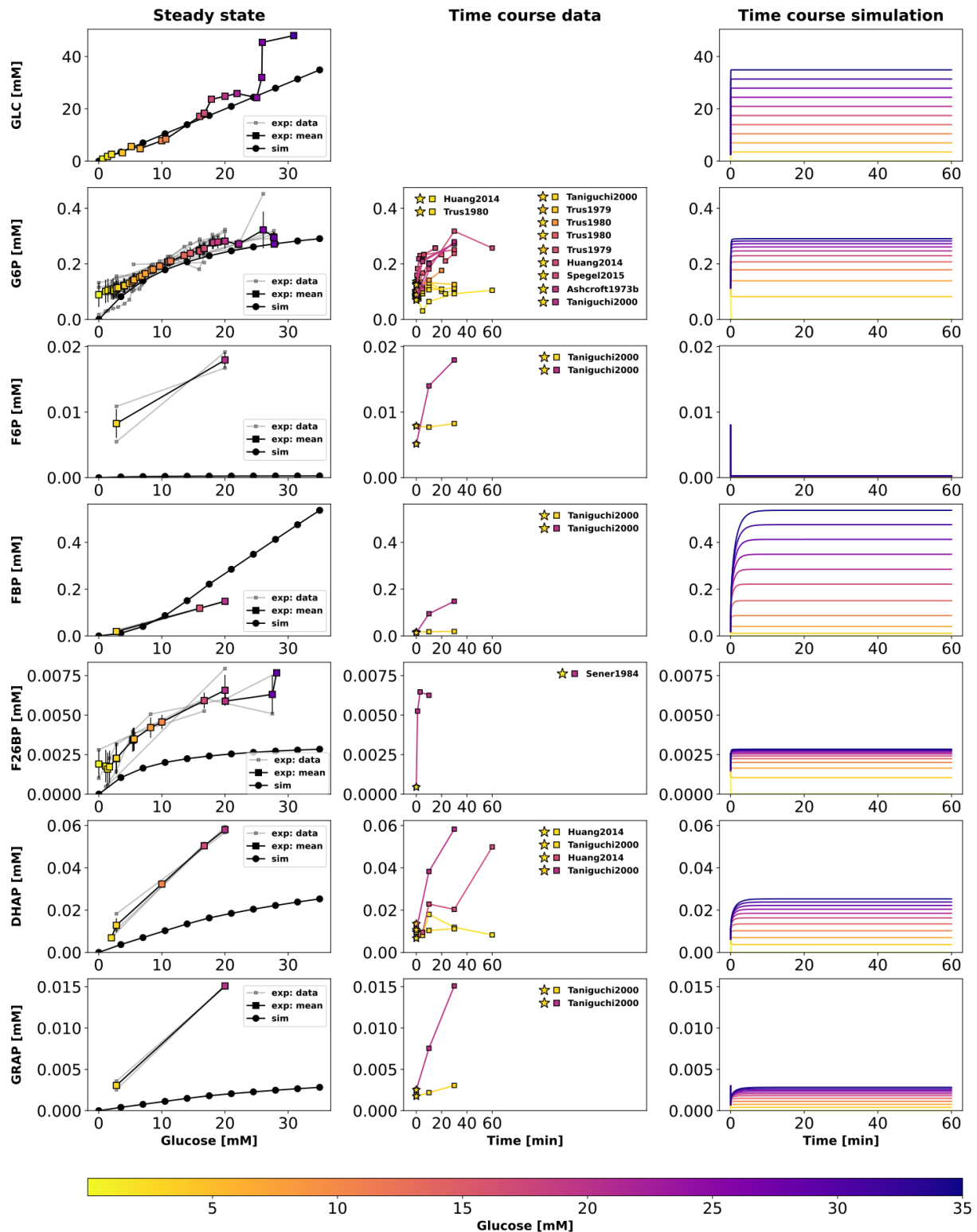


Figure 5. Effect of variations in blood glucose on glycolytic intermediates. (left column) Dose-response simulations. Glucose scan was performed for the calculation of steady-state concentration of metabolites in the model. The steady-state concentrations predicted by the model at various glucose doses were compared with the normalized values of experimental measurements; (middle column) Time course experimental data. Time course values of glycolytic intermediates and cofactors from multiple experimental studies carried out at different incubation doses of glucose; (\star) in the legend indicates the pre-incubation glucose dose. (right column) Time course simulations. The effect of variation in blood glucose dose on the transient concentration of metabolites. GLC: glucose, G6P: glucose 6-phosphate, F6P: fructose 6-phosphate, FBP: fructose 1,6-bisphosphate, F26BP: fructose 2,6-bisphosphate, DHAP: dihydroxyacetone phosphate, GRAP: glyceraldehyde 3-phosphate. Data from (Akhtar et al., 1977; Ashcroft et al., 1970, 1973b; Giroix et al., 1984; Huang and Joseph, 2014; Liu et al., 1998, 2004; Malmgren et al., 2013; Matschinsky and Ellerman, 1968; Miwa et al., 2000; Spégel et al., 2015; Sener et al., 1984; Taniguchi et al., 2000; Trus et al., 1979, 1980).

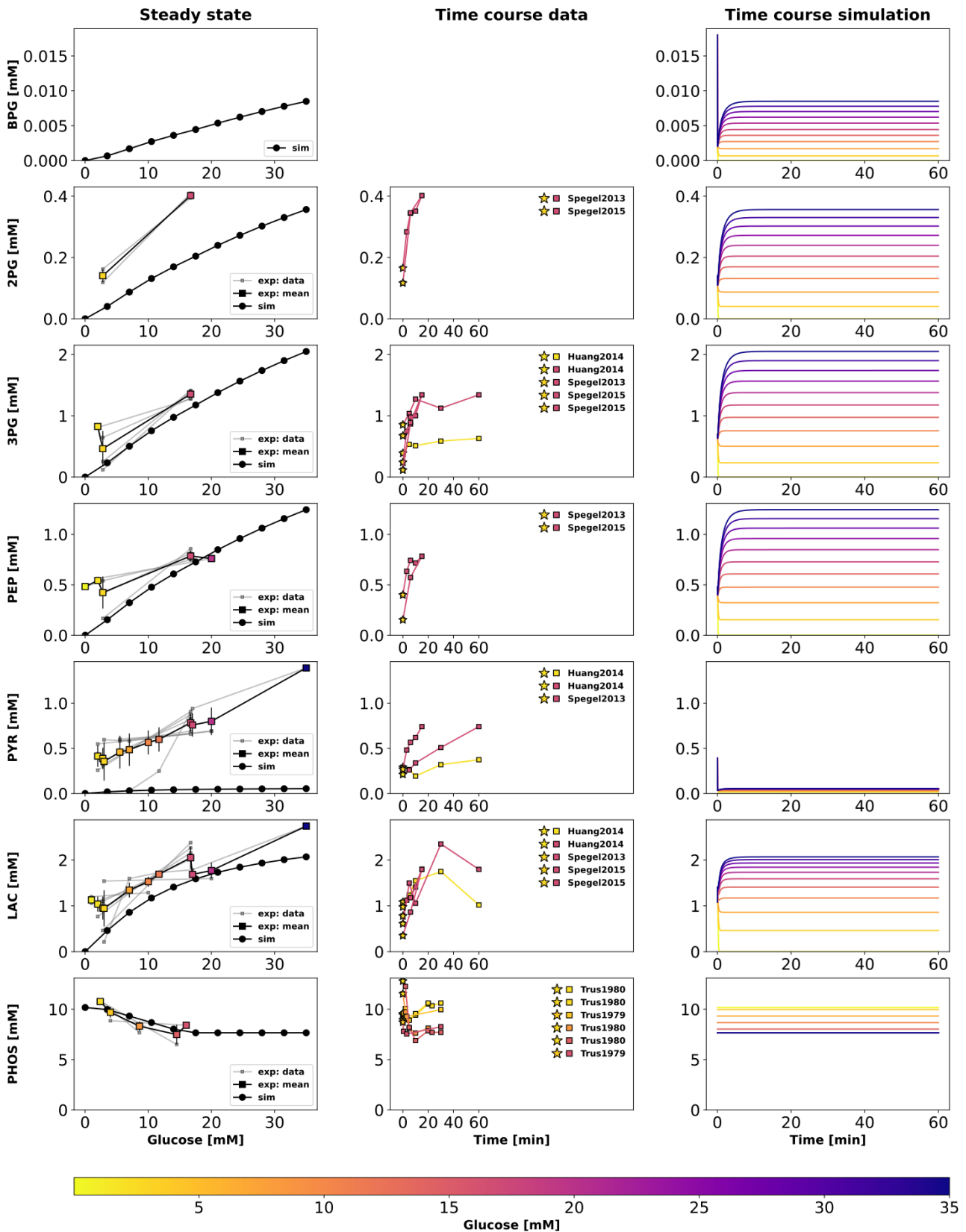


Figure 6. Effect of variations in blood glucose on glycolytic intermediates. The plot is analogous to Fig. 5. BPG: 1,3-biphosphoglycerate, 2PG: 2-phosphoglycerate, 3PG: 3-phosphoglycerate, PEP: phosphoenolpyruvate, PYR: pyruvate, LAC: lactate, PHOS: phosphate. Data from (Ashcroft and Christie, 1979; Ewart et al., 1983; Guay et al., 2013; Hedekov et al., 1987; Huang and Joseph, 2014; Malinowski et al., 2020; Malmgren et al., 2013; Spéjel et al., 2013, 2015; Sugden and Ashcroft, 1977; Trus et al., 1979, 1980).

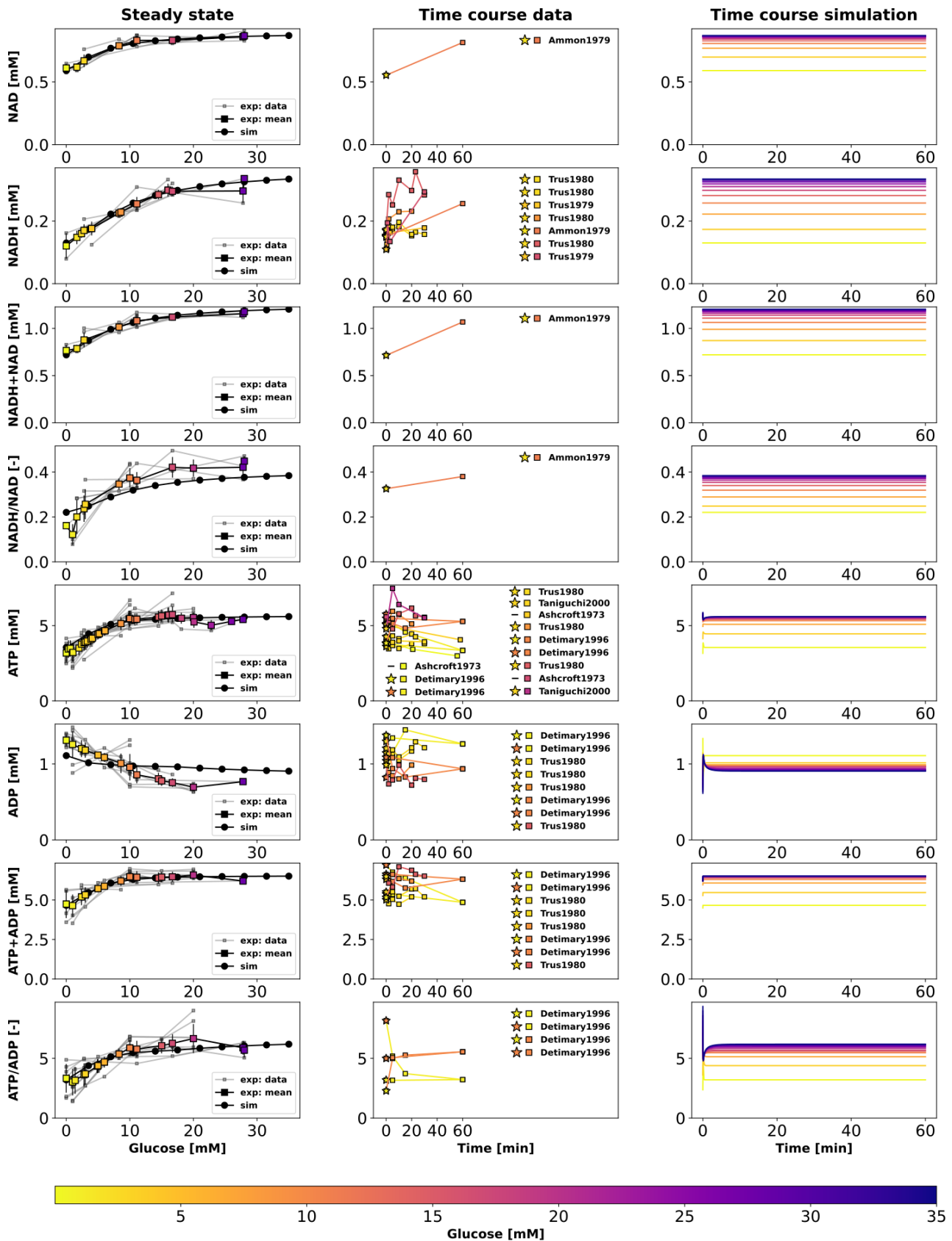


Figure 7. Effect of variations in blood glucose on glycolytic cofactors. The plot is analogous to Fig. 5. NAD: nicotinamide adenine dinucleotide, NADH: nicotinamide adenine dinucleotide reduced. ATP: adenosine triphosphate, ADP: adenosine diphosphate Data from (Ammon et al., 1979, 1998; Ashcroft et al., 1970; Detimary et al., 1996, 1998; Guay et al., 2013; Hedekov et al., 1987; Lamontagne et al., 2009; Malaisse et al., 1978; Malaisse and Sener, 1987; Matschinsky and Ellerman, 1968; Matschinsky et al., 1976; Sener et al., 1978; Spégel et al., 2015; Taniguchi et al., 2000; Trus et al., 1979, 1980).

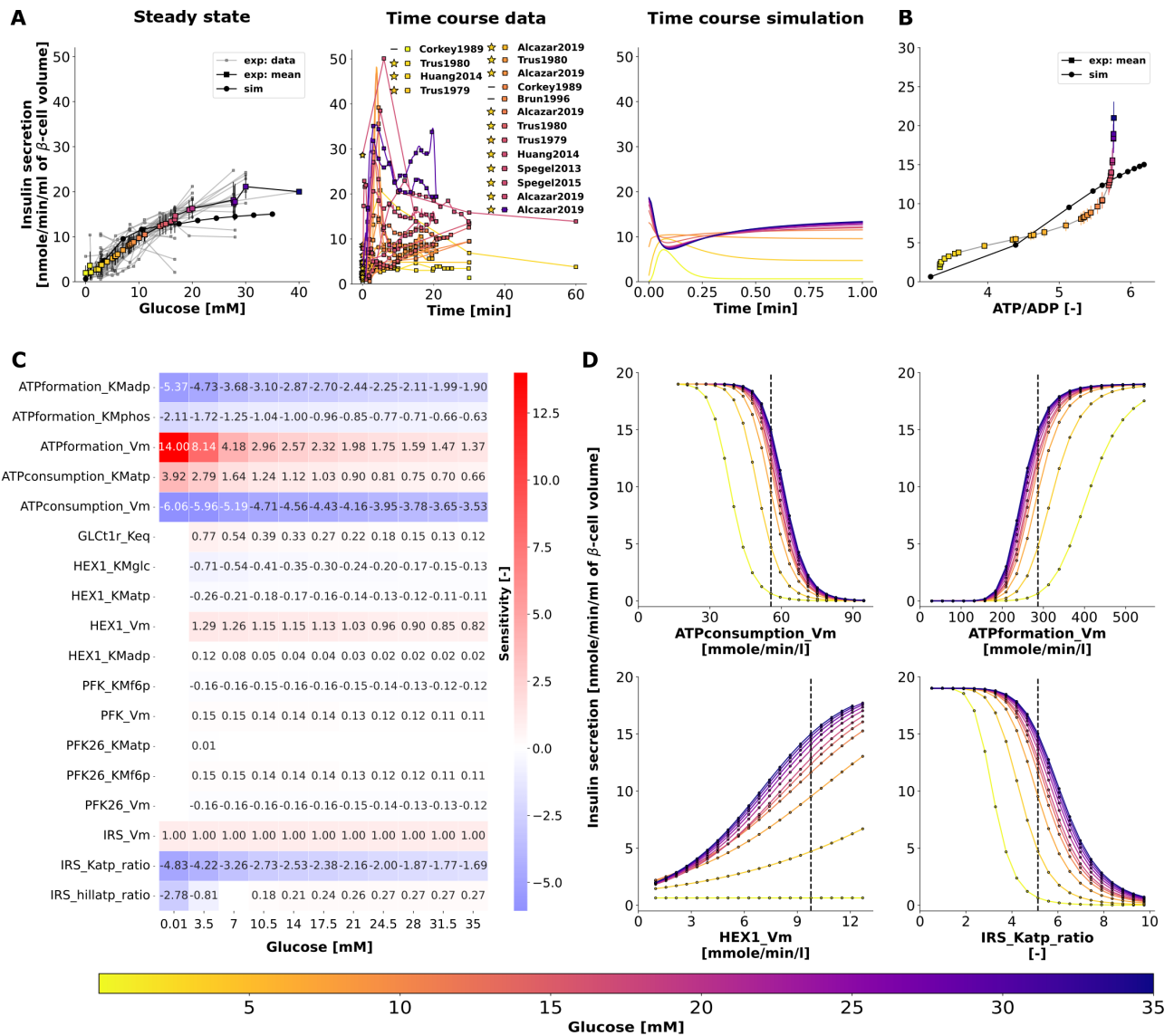


Figure 8. (A) Effect of variations in blood glucose on insulin secretion. The plot is analogous to Fig. 5. Data from (Alcazar and Buchwald, 2019; Ammon et al., 1998; Ashcroft et al., 1973a; Brun et al., 1996; Corkey et al., 1989; Detimary et al., 1996, 1998; Ewart et al., 1983; Guay et al., 2013; Hedekov et al., 1987; Huang and Joseph, 2014; Johnson et al., 2007; Lamontagne et al., 2009; Liu et al., 1998, 2004; Meglasson and Matschinsky, 1986; Sener et al., 1978; Spéjel et al., 2013, 2015; Trus et al., 1979, 1980; Xu et al., 2008a,b). **(B) Effect of change in energy state (ATP/ADP ratio) of the β -cell on insulin secretion.** The rate of insulin release in response to changes in ATP/ADP ratio is shown. **(C) Sensitivity analysis indicating the effect of perturbation in model parameters on insulin secretion.** Heatmap illustrating the values of scaled local sensitivities illustrating the effect of parameter perturbations on the amount of insulin secretion at varying glucose doses. Highly sensitive values are colored in red and blue. The parameters which cause less than 1% change in insulin response for 10% perturbation were not displayed for clarity. For more details, please refer to Sec. 2.6. **(D) Effect of change in model parameters on insulin secretion as a function of glucose dose.** The rate of insulin secretion in response to perturbation in the values of ATPconsumption_Vm, HEX1_Vm, IRS_Katp_ratio, IRS_hillKatp_ratio. The vertical line indicates the model value.