Spatial cumulant models enable spatially informed treatment strategies and analysis of local interactions in cancer systems

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Abstract

Theoretical and applied cancer studies that use individual-based models (IBMs) have been limited by the lack of a mathematical formulation that enables rigorous analysis of these models. However, spatial cumulant models (SCMs), which have arisen from recent advances in theoretical ecology, can be used to describe population dynamics generated by a specific family of IBMs, namely spatio-temporal point processes (STPPs). SCMs are spatially resolved population models formulated by a system of ordinary differential equations that approximate the dynamics of two STPP-generated summary statistics: first order spatial cumulants (densities), and second order spatial cumulants (spatial covariances).

Here, we exemplify how SCMs can be used in mathematical oncology by modelling a theoretical cancer cell population comprising interacting growth factor producing and non-producing cells. To formulate our models, we use the `Unified Framework Software` which was recently developed by Cornell *et al.* (2019) and enables the generation of STPPs, SCMs and mean-field population models (MFPMs) from user-defined model descriptions. Our results demonstrate that SCMs can capture STPP-generated population density dynamics, even when MFPMs fail to do so. From both MFPM and SCM equations, we derive treatment-induced cell death rates required to achieve non-growing cell populations. When testing these treatment strategies in STPP-generated cell populations, our results demonstrate that SCM-informed strategies outperform MFPM-informed strategies in terms of inhibiting population growths. We argue that SCMs provide a new framework in which to study cell-cell interactions, and can be used to deepen the mathematical analysis of IBMs and thereby increase IBMs' applicability in cancer research.

1 Introduction

All biological systems are composed of interacting parts. In cancer systems, cells can interact with each other by, for example, exchanging signalling molecules and competing for resources such as space and nutrients. Such cell-cell interactions have been identified as factors that drive eco-evolutionary dynamics of cancer cell populations (Merlo et al., 2006; Reynolds et al., 2020). Consequently, these interactions have been proposed as cancer treatment targets, where the general premise is that treatments can perturb cell-cell interactions and, by extension, disease trajectories. Such perturbations can lead to reduced tumour growths and disease burdens (Zhang et al., 2017; Dominiak et al., 2020; Brücher and Jamall, 2014; West and Newton, 2019). Cell-cell interactions, and the impact that they have on cancer system dynamics, have been mathematically studied by researchers using a variety of mathematical models including evolutionary game theory (EGT) models (Zhang et al., 2017; Kaznatcheev et al., 2019; Archetti et al., 2015), other ordinary differential equation (ODE) models (Hillen et al., 2013; Poleszczuk and Enderling, 2018; Jenner et al., 2018), partial differential equation (PDE) models (Haridas et al., 2017; Lorenzi et al., 2017; Hinow et al., 2009), and individual-based models (IMBs) (Stichel et al., 2017; Campenni et al., 2020; Hamis et al., 2021).

In IBMs, cells can be modelled as individuals that evolve on a spatial domain and partake in interactions with other cells in their neighbourhood (Metzcar et al., 2019; Chamseddine and Rejniak, 2020). IBMs are naturally able to incorporate local cell-cell interactions, spatial population structures and stochastic variations between cells and biological events. However, theoretical and experimental studies that use IBMs have been limited by the lack of a mathematical formulation that enables rigorous analyses of these models. On the other hand, in mean-field population models (MFPMs), including ODE and EGT models, the density dynamics of cancer cell subpopulations can be described by a set of mathematically tractable ODEs after imposing a set of simplifying modelling assumptions. In such models, cells are not considered as individuals, but instead they are collectively treated as part of a population or subpopulation. With their analytical and mathematically tractable formulation, MFPMs have been used to quantify cell-cell interactions in *in vitro* experiments (Kaznatcheev et al., 2019), and are currently being used to inform personalised treatment strategies in a clinical prostate cancer trial (Zhang et al., 2017). However, MFPMs notably assume that the modelled system is "well-mixed", so that each cell interacts with all other cells in the system with equal probability. Therefore, MFPMs can not faithfully capture the dynamics of spatially structured systems with localised cell-cell interactions, such as solid tumours (Waclaw et al., 2015). In fact, previous mathematical modelling work has shown that imposing spatial constraints on interactions between individuals, via IBMs, often results in system dynamics that vastly contradicts that simulated by MFPMs (Durrett and Levin, 1994).

Due to the pre-clinical and clinical applications of mathematical oncology models (Rockne et al., 2019), there exists a need to formulate models that capture localised cell-cell interactions and are both spatially resolved and mathematically tractable. In this article, we describe an approach to achieve this by using spatial cumulant models (SCMs) which, to our knowledge, have not previously been applied to study cancer cell systems. SCMs are spatially resolved population models that are translated from a specific family of IBMs, namely spatio-temporal point processes (STPPs). Following a mathematical manipulation that involves a perturbation expansion around mean-field equations in the limit of long-ranged interactions (as explained in Section 2), SCMs approximate two STPP-generated summary statistics: first order spatial cumulants (densities) and second order spatial cumulants (spatial covariances). If we let $u_i^{(1)}(t)$ denote the density of subpopulation i, and $u_{ij}^{(2)}(t,r)$ denote the spatial covariance of individuals (here cells) from subpopulations i and j, then SCMs dictate that

$$\underbrace{u_i^{(1)}(t)}_{density} = \underbrace{q_i(t)}_{\substack{mean\text{-}field\\density}} + \epsilon^d \underbrace{p_i(t)}_{\substack{correction\\density}} + o(\epsilon^d), \tag{1a}$$

$$\underbrace{u_{ij}^{(2)}(t,r)}_{spatial\ covariance} = \epsilon^d \underbrace{g_{ij}(t,\epsilon r)}_{\substack{leading\ term\ of\ the\\spatial\ covariance}} + o(\epsilon^d), \tag{1b}$$

where t is the independent time variable and r denotes pair-wise distances between individuals. In Eq.8a, $q_i(t)$ denotes the density as computed by MFPMs and $p_i(t)$ is a correction term that depends on (1) the MFPM densities $q_i(t)$, (2) the leading spatial covariance terms $g_{ij}(t,\epsilon r)$, and (3) all corrections $p_i(t)$, where $i,j = 1,..,S$ and S denotes the number of subpopulations in the modelled system. Thus the correction terms account for the spatial structure of the population via their dependence on $g_{ij}(t,\epsilon r)$. The modelled individuals inhabit a d-dimensional spatial domain, and the scaling factor $\epsilon = 1/\ell$, $\ell > 0$, results from the perturbation expansion, where ℓ is a typical interaction length scale, so that SCM densities reduce

to MFPM densities when $\ell \to \infty$. The terms $o(\epsilon^d)$ can be omitted in practical applications as they go to zero faster than does ϵ^d.

SCMs where first presented as a rigorous mathematical framework by Ovaskainen *et al.* (2014). The models build upon earlier studies of spatial moment equations in theoretical ecology (Ovaskainen and Cornell, 2006; Bolker and Pacala, 1997; Law et al., 2003) and probability theory (Finkelshtein et al., 2009; Kondratiev et al., 2008), and on probability theorists' work on STPPs, also known as "Markov evolutions in the space of locally finite configurations", (Kondratiev and Skorokhod, 2011; Finkelshtein et al., 2011). We also remark that other spatial moment approaches, that are similar to SCMs, have been used to derive deterministic approximations to the dynamics of IBMs describing cell systems (Binny et al., 2016).

Since Eqs.1(a,b) are formulated in the limit of long-ranged interactions it follows that, in the context of cancer research, SCMs are appropriate to use when studying cell-cell interactions that extend beyond only immediately neighbouring cells. Such interactions include communication via diffusible substrates and resource competition. Formulating the right-hand-sides of Eqs.1(a,b) for a specific biological problem can be a mathematically cumbersome task. However, Cornell *et al.* (2019) developed a mathematical framework and a computational software that enables the generation of rate equations for the quantities q_i, p_i and g_{ij} for a large family of biological processes. More specifically, the software enables the generation of (1) STPPs and (2) MFPM and SCM rate equations for any user-defined biological system that can be described by one or more reactant-catalyst-product (RCP) processes. An RCP-processes is formulated by a set of reactants (that are consumed in the process), catalysts (that catalyse the process without being consumed in it), and products (that are produced in the process). Cornell *et al.*'s framework thus unifies a class of IBMs, *i.e.* STPPs, with a class of analytical and spatially structured population models, *i.e.* SCMs. Accordingly, we refer to their software as the `Unified Framework (UF) Software` throughout this article.

This article is structured as follows: In Section 2, we provide an introductory description of the mathematical theory that underlies SCMs and the `UF-Software`. In Section 3.1, we propose a practical step-by-step pipeline for to use the `UF-Software` to implement STPPs, MFMPs and SCMs. Thereafter, as proof-of-concept, we exemplify how SCMs and the `UF-Software` can be used in mathematical cancer research by modelling dynamic, spatially structured cancer cell populations in which cells communicate via diffusible substrates and are subjected to drugs (Sections 3.2-4.2).

2 Mathematical theory of spatial cumulant models

Sections 2.1-2.10 are intended to comprise an introductory and self-contained background to SCMs. For more rigorous details of this mathematical theory, we refer readers to previous works (Ovaskainen and Cornell, 2006; Ovaskainen et al., 2014; Cornell et al., 2019). For ease of presentation we, throughout this article, consider spatial domains that are two-dimensional and have periodic boundary conditions. Moreover, we consider systems that are translationally invariant, meaning that pair-wise distances between cells influence system dynamics, whereas absolute positions of cells do not. This is equivalent to modelling a space-homogeneous system that lacks background variations, such as a typical *in vitro* system. Note, however, that the `UF-Software` can be modified to handle one, two, and three dimensional spatial domains, as well as space-heterogeneous systems (Cornell et al., 2019).

2.1 Spatio-temporal point patterns and spatio-temporal point processes

Consider a cell population that evolves in time and space. A snapshot of the population can be represented by a point pattern in which the midpoint of the nth cell is represented by a point $x_n \in D$, where $D \subset \mathbb{R}^d$ denotes the spatial domain that the population inhabits. In this article, we set D to be a plane spanning two spatial dimensions, so that $d = 2$ and $x_n = (x_n^1, x_n^2)$. A point pattern comprising N_t points at time t can thus be described by a set of points η_t in continuous space such that

$$\eta_t = \{x_1, x_2, ..., x_{N_t}\}. \tag{2}$$

In order to categorise the individuals in the population, each point in η_t can further be coupled with a descriptive mark. Here, we let the mark m_n denote the subpopulation to which the individual in position x_n belongs, so that m_n can take the value $1, 2, ..., S$, where S denotes the number of subpopulations in the modelled system. When marks are included, a point pattern describing a population snapshot can thus be described by a set of marked points

$$\hat{\eta}_t = \{\{x_1, m_1\}, \{x_2, m_2\}, ..., \{x_{N_t}, m_{N_t}\}\}. \tag{3}$$

A point pattern can be compactly described in terms of its densities and spatial covariances. Information on how to calculate these quantities from static point patterns are provided in Section 2.9. A point pattern that evolves in time and space is called a spatio-temporal point pattern, and an STPP is mathematical model that can generate spatio-temporal point patterns in continuous time and continuous space. Intuitively, an STPP can be thought of as a collection of stochastic processes that makes points appear or disappear from $\hat{\eta}$. In the context of cell biology, such processes can, for example, describe cell division, cell movement and cell death.

2.2 A verbal description of the relationship between spatio-temporal point processes and spatial cumulant models

The STPP rules that govern the evolution of spatio-temporal point patterns are of a stochastic nature. Therefore, a general STPP can generate an ensemble of different realisations, *i.e.* spatio-temporal point patterns, for a given initial cell configuration. It is, in general, impossible to predict how one specific realisation will evolve in time and space. However, if we generate multiple STPP realisations, then SCMs can be used to deterministically approximate how densities and spatial covariances will evolve on average for the realisations.

2.3 Reactant-catalyst-product processes and interaction kernels

The `UF-Software` can generate STPPs, MFPMs and SCMs for any biological system that can be described by one or more of RCP-processes. For example, density independent cell division can be described as an RCP-process where a cell of mark m in location x_v produces a daughter cell with the same mark in location x_w, so that $\{x_v,m\}$ is a catalyst and $\{x_w,m\}$ is a product. Similarly, if a cell in location x_v with mark m moves to location x_u, then $\{x_v,m\}$ is a reactant and $\{x_u,m)$ is a product, and if a cell in location x_v of mark m dies, then $\{x_v,m\}$ is a reactant. RCP-processes that include only one point are associated with model parameters that do not depend on distances to other points. Such processes can, for example, describe density independent cell deaths, or spontaneous cell-type conversions, which are associated with model parameters describing the rates (probability per time unit) at which they occur. RCP-processes that include two or more points are associated with spatial kernels that have a total integral and a probability distribution. The kernels describe rates at which RCP-process events occur, as a function of pair-wise distances between cells. If we, for example, consider density-dependent cell birth, where a cell of mark n causes a cell of mark m to divide, then we have two catalyst ($\{x_v,m\}$ and $\{x_{v'},n\}$) and one product ($\{x_w,m\}$). This RCP-process is then governed by an interaction kernel that is a function of the distance between v and v', and a daughter cell dispersal kernel that is a function of the distance between v and w. Note that all RCP-interactions are pair-wise interactions, and thus the rate at which density dependent RCP-process events occur are generally determined by multiple pair-wise interactions.

The `UF-Software` includes two pre-defined, radially symmetric, kernels, being the Gaussian kernel a_{G} and the Top-Hat kernel a_{TH} such that, on a two-dimensional domain,

$$a_{\mathrm{G}}[I,\sigma](r) = \frac{I}{2\pi\sigma^2} e^{\frac{-r^2}{2\sigma^2}} \tag{4}$$

and

$$a_{\mathrm{TH}}[I,r_0](r) = \frac{I}{\pi r_0^2} \quad \text{if} \quad r \leq r_0, \tag{5a}$$

$$a_{\mathrm{TH}}[I,r_0](r) = 0 \qquad \text{if} \quad r > r_0. \tag{5b}$$

Here I denotes the total integral of the interaction kernel, σ is one kernel standard deviation, r_0 is a kernel interaction radius, and r is the distance between two interacting individuals (cells).

2.4 Spatial moments and cumulants

The spatial cumulants are closely related to the spatial moments (which are also called correlation functions). The first spatial moment, $k^{(1)}(x)$, measures the expected density of individuals at location x. It follows that the expected number of individuals on an area Λ at time t can be calculated by

$$E(|\gamma_t \cap \Lambda|) = \int_{\Lambda} k_t^{(1)}(x)dx, \tag{6}$$

where γ_t is a point configuration. The second spatial moment, $k^{(2)}(x_1, x_2)$, can similarly be used to calculate the product of 'the number of individuals in area Λ_1' and 'the number of individuals in area Λ_2', such that

$$E(|\gamma_t \cap \Lambda_1||\gamma_t \cap \Lambda_2|) = \int_{\Lambda_1}\int_{\Lambda_2} k_t^{(2)}(x_1, x_2)dx_1dx_2 + \int_{\Lambda_1\cap\Lambda_2} k_t^{(1)}(x)dx, \tag{7}$$

where the last term has been included on order to handle self-pairs (Ovaskainen et al., 2020). The first and second order spatial cumulants are respectively denoted by $u_i^{(1)}(x)$ and $u_{ij}^{(2)}(x_1, x_2)$, where

$$u_i^{(1)}(x) = k_i^{(1)}(x), \tag{8a}$$

$$u_{ij}^{(2)}(x_1, x_2) = k_{ij}^{(2)}(x_1, x_2) - k_i^{(1)}(x_1)k_j^{(1)}(x_2). \tag{8b}$$

Here, the subscripts i and j have been included to denote different subpopulations in the modelled system, so that $i, j = 1, .., S$, where S denotes the number of modelled subpopulations. From Eqs.8(a,b) it is clear that the first and second order spatial moments and cumulants carry the same information. To then understand why cumulants have been introduced, note first that spatial moments (and cumulants) can be defined up to any order, and that dynamical systems of spatial moments (and cumulants) generally are unclosed. This means that the equations describing spatial moment (or cumulant) dynamics generally depend on higher order spatial moments (or cumulants), making them impossible to solve without enforcing some sort of closure scheme in which spatial moments (or cumulants) of order $v + 1$ are approximated in terms of spatial moments (or cumulants) up to order v. However, after a perturbation expansion (Section 2.6) and a model rescaling (Section 2.7), the spatial cumulant formulation enables the derivation of approximate equations in closed form that describe the dynamics of the first and second order spatial cumulants for RCP-formulated STPPs.

2.5 The relationship between Markov operators and operators for spatial cumulant rate equations

If we let F denote a real-valued function that describes some quantity of an STPP-generated realisation γ, and μ denotes a probability measure on Γ, then

$$\langle F, \mu\rangle := \int_\Gamma F(\gamma)d\mu(\gamma), \tag{9}$$

describes the value of F averaged over all realisations $\gamma \in \Gamma$. The rate of change of the pairing $\langle F, \mu\rangle$ can then be obtained by

$$\frac{d}{dt}\langle F, \mu(t)\rangle := \langle LF, \mu(t)\rangle, \tag{10}$$

where L is Markov operator, that acts on F and describes a process that causes points to appear on, or disappear from, a set of points $\hat{\eta}$. In order to describe a cell population that is governed by B biological processes (here, RCP-processes), the model's total Markov operator can be written as a linear combination of Markov operators L_b such that

$$L = \sum_{b=1}^{B} L_b. \tag{11}$$

For any such Markov operator L, there exists a corresponding operator L^Δ that describes the time evolution of spatial moments of any order such that

$$\frac{d}{dt}k(t, \eta) = (L^\Delta k)(t, \eta), \tag{12}$$

where L^Δ is a linear function of interaction kernels and η. Similarly, a Markov operator L be mapped to an operator Q^Δ that describes the time evolution of spatial cumulants of any order such that

$$\frac{d}{dt}u(t, \eta) = (Q^\Delta u)(t, \eta), \tag{13}$$

where Q^Δ is a sum of the linear term L^Δ and a non-linear term M^Δ,

$$Q^\Delta = L^\Delta + M^\Delta. \tag{14}$$

Deriving the operators L^Δ and Q^Δ from a Markov operator L can be a mathematically challenging and laborious task. However, for any system of RCP-processes, the `UF-Software` can handle the formulation of L, L^Δ and Q^Δ "under-the-hood".

2.6 The perturbation expansion

As a first step towards circumventing the problem of moment closure, Ovaskainen and Cornell (2006) proposed using a perturbation expansion in which interactions between points are considered to be long-ranged (but not global). Markov operators L (Eq.11) are generally described with the help of interaction kernels $a(x)$ (Section 2.3). In the limit of long-ranged interactions, Ovaskainen *et al.* (2006) introduced a rescaled form of Markov operators L_ϵ that are described by scaled interaction kernels $a_\epsilon(x)$, such that

$$a_\epsilon(x) := \epsilon^d a(\epsilon x). \tag{15}$$

The integrals of $a(x)$ and $a_\epsilon(x)$ over $\mathbb{R}^d$ have the same value, but when $\epsilon \to 0$, the scaled interaction kernels becomes increasingly long-ranged and flat so that each individuals interact with an increasing number of other individuals. In the proposed perturbation expansion, the population density $k^{(1)}(t)$ was expressed as

$$k^{(1)}(t) = q(t) + \epsilon^d p(t) + \epsilon^{2d} s(t) + \dots \ , \tag{16}$$

where $\epsilon = 1/\ell$ and ℓ denotes the characteristic interaction length-scale, $q(t)$ is the density computed by MFPMs, and higher order terms $p(t), s(t), \dots$ are correction terms that account for the spatial structure of the modelled population. From Eq.16, we can see that this perturbation expansion has two practical advantages: (1) the calculated density $k^{(1)}(t)$ tends to the mean-field density when $\epsilon \to 0$, and (2) if we calculate $k^{(1)}(t)$ with correction terms up to the nth order, then we know beforehand that the error will behave as $O(\epsilon^{(n+1)d})$. The correction terms $p, s, \dots$ in Eq.16 can in principle be derived up to arbitrarily high orders, but truncating the perturbation expansion after one correction terms yields

$$k^{(1)}(t) = q(t) + \epsilon^d p(t) + O(\epsilon^{2d}). \tag{17}$$

Ovaskainen and Cornell 2019 derived the expressions for $q(t)$ and $p(t)$ for a specific biological system. Based on their results, they concluded that including only one correction term in the density calculation (Eq.17) is expected to suffice to capture STPP dynamics for many practical applications. Building on the heuristic work presented in 2006, Ovaskainen *et al.* later (2014) developed a rigorous mathematical framework for deriving spatial moment and cumulant rate equations from Markov operators, where the authors expected that spatial cumulants (of any orders) could be expressed as

$$u(t, \eta) = v(t, \eta) + \epsilon^d w(t, \eta) + o(\epsilon^d), \tag{18}$$

where v is a mean-field term and w is a first order correction term. Thus if we can find v and w, expressions for spatial cumulants can be obtained. In 2019, Cornell *et al.* presented the `UF-Software` which enables the derivation of v and w for the first two spatial cumulants (densities and spatial covariances) for any system that is described by RCP-processes.

2.7 The model rescaling

In Eq.12, moment dynamics is described using an operator L^Δ. Analogously, in the limit of long ranged interactions, a scaled operator L_ϵ^Δ is introduced such that

$$\frac{\partial}{\partial t}\hat{k}_{\epsilon,t}(\eta) = (L_\epsilon^\Delta \hat{k}_{\epsilon,t})(\eta), \tag{19}$$

where the hat-notation here denotes scaled solutions to the spatial moments. Ovaskainen *et al.* (2014) remarked that the full model describing population dynamics should satisfy two important properties in order be practical and realistic in applications: (1) when the interaction length ℓ goes to infinity, the model dynamics should tend to MFPM dynamics, as each individual will interact with an increasing number of other individuals, and (2) the spatial clustering or spread of the individuals should scale with ℓ, *i.e.,* the model should scale with respect to space. The authors therefore introduced a scaling operator S_c that rescales a point configuration η such that

$$(S_c k)(\eta) := k(c\eta), \tag{20}$$

where

$$c\eta := \{cx | x \in \eta\}. \tag{21}$$

A renormalised version of the operator L_ϵ^Δ, acting on $k_{\epsilon,t}(\eta)$, can then be defined as

$$L_{\epsilon,\text{ren}}^\Delta := S_{\epsilon^{-1}} L_\epsilon^\Delta S_\epsilon \tag{22}$$

so that

$$\frac{\partial}{\partial t} k_{\epsilon,t}(\eta) = (L_{\epsilon,ren}^\Delta k_{\epsilon,t})(\eta) = (S_{\epsilon^{-1}} L_\epsilon^\Delta S_\epsilon k_{\epsilon,t})(\eta) = (S_{\epsilon^{-1}} L_\epsilon^\Delta k_{\epsilon,t})(\epsilon\eta) \Longrightarrow$$

$$\Longrightarrow S_\epsilon \frac{\partial}{\partial t} k_{\epsilon,t}(\eta) = (L_\epsilon^\Delta k_{\epsilon,t})(\epsilon\eta)$$

and thus,

$$\frac{\partial}{\partial t} k_{\epsilon,t}(\epsilon\eta) = (L_\epsilon^\Delta k_{\epsilon,t})(\epsilon\eta). \tag{23}$$

Since $\hat{k}_{\epsilon,t}$ in Eq.19 (a simulation-generated estimate of the spatial moment) and $k_{\epsilon,t}$ in Eq.23 (an analytical expression of the spatial moment) should generate the same system dynamics, this means that

$$\hat{k}_{\epsilon,t}(\eta) = k_{\epsilon,t}(\epsilon\eta). \tag{24}$$

From Eq.23, it follows that the rate equations for spatial cumulants take the form

$$\frac{\partial}{\partial t} u_{\epsilon,t}(\epsilon\eta) = (Q_\epsilon^\Delta u_{\epsilon,t})(\epsilon\eta), \tag{25}$$

into which we can insert the assumed form of the spatial cumulants in the limit of long ranged interactios (Eq.18). If we do this, and the operator Q^Δ is known, we can solve for the functions v and w in Eq.18. When doing this, the dynamical system is still unclosed so that $u_{\epsilon,t}^{(n)}$ depends on higher order spatial cumulants but, when solving for v and w, algebraic manipulation will show that $u_{\epsilon,t}^{(n)} = o(\epsilon^d)$ for $n > 2$, and thus can be ignored. The `UF-Software` can generate analytical expressions for v and w for the first and second order spatio-temporal cumalants from any model description formulated by one or more RCP-processes. Thus, when using the `UF-Software`, a user does not need to derive any operators, or perform any algebraic calculations to obtain mathematical expressions for the functions v and w.

2.8 Spatial cumulant model equations

The `UF-Software` formulates the terms v and w (Eq.18) in terms of three auxiliary functions: q_i, p_i and g_{ij} which are used to approximate the first and second order spatial cumulants (Eq.1). More precisely, the `UF-Software` generates the right-hand-sides of the ODEs

$$\begin{cases} \frac{d}{dt} q_i = H_{q_i}, & \text{(26a)} \\ \frac{d}{dt} p_i = H_{p_i}, & \text{(26b)} \\ \frac{d}{dt} g_{ij} = H_{g_{ij}}, & \text{(26c)} \end{cases}$$

where $H_{q_i}, H_{p_i}, H_{g_{ij}}$ are exact expressions (Cornell et al., 2019). These expressions are calculated for all $i, j = 1, .., S$, where S denotes the number of subpopulations in the system. The expressions H_{q_i} generally depend on all subpopulation densities $q_1(t), ..., q_S(t)$. Similarly, the expressions $H_{g_{ij}}$ generally depend on all densities and leading spatial covariance terms g_{ij}. Lastly, the correction expressions H_{p_i} generally depend all densities, leading spatial covariance terms and correction terms $p_i(t)$.

In order to calculate SCMs in practice, first use the `UF-Software` to generate the the expressions for $H_{q_i}, H_{p_i}, H_{g_{ij}}$. Thereafter, we use the pipeline codes developed for this study (Section 3.1) to numerically solve for the quantities q_i, p_i, g_{ij}. By inserting the numerical values of q_i, p_i, g_{ij} into Eqs.1(a,b), densities and spatial covariances can be obtained. Note that, for many RCP-processes, the expressions for g_{ij} include convolution integrals, which are easier to work with in Fourier space than in real space. Therefore, `UF-Software`-generated expressions for $H_{g_{ij}}$ generally include Fourier transforms of interaction kernels and variables g_{ij}.

2.9 Calculating spatial moments and cumulants from point patterns

In the space-homogenous case, the static first order spatial moment, $k^{(1)}_{i,T}$, and cumulant, $u^{(1)}_{i,T}$, of subpopulation i at time T be directly calculated from a point pattern as

$$k^{(1)}_{i,T} = u^{(1)}_{i,T} = \frac{N_{i,T}}{A}, \tag{27}$$

where $N_{i,T}$ denotes the number of type i individuals on domain D with area A. Static second order spatial moments at time T can be approximated from a point pattern by

$$k^{(2)}_{ij,T}(z) = \frac{1}{A}\int_D \rho_i(x)\rho_j(x+z)dx, \tag{28}$$

where ρ_i denotes the density of subpopulation i and z is a spatial displacement, so that $z = (z^1, z^2)$ when D is two-dimensional (Dieckmann et al., 2000). The pair densities $k^{(2)}_{ij,T}(z)$ are also called auto-correlations (for $i = j$) and cross-correlations (for $i \neq j$). When approximating static second order spatial moments for space-homogenous systems, the magnitude $r = |z|$ of the displacement in Eq.28 is of importance, whereas the direction of z is not. In practical applications, we can thus construct a vector

$$\mathbf{k^{(2)}_{ij,T}} = \Big(k^{(2)}_{ij,T}(r_0),\quad k^{(2)}_{ij,T}(r_{\Delta h}),\quad k^{(2)}_{ij,T}(r_{2\Delta h}),\quad \ldots\ \Big), \tag{29}$$

for some displacement-magnitude step size Δh, where each vector element $k^{(2)}_{ij,T}(r_\zeta)$ describes the density of (type i)-(type j) cell pairs that are separated by a distance $r \in [r_\zeta,\ r_\zeta + \Delta h)$. Following Eq.8b, static second order spatial cumulants can be approximated by subtracting densities (Eq.28) from pair-densities Eq.29. Then, analogously to Eq.29, static second order spatial cumulants can, in translationally invariant cases, be compactly approximated by a vector

$$\begin{aligned}\mathbf{u^{(2)}_{ij,T}} &= \Big(u^{(2)}_{ij,T}(r_0),\quad u^{(2)}_{ij,T}(r_{\Delta h}),\quad u^{(2)}_{ij,T}(r_{2\Delta h}),\quad \ldots\Big) = \\ \epsilon^d\mathbf{g_{ij,T}} &= \epsilon^d\Big(g_{ij,T}(\epsilon r_0),\quad g_{ij,T}(\epsilon r_{\Delta h}),\quad g_{ij,T}(\epsilon r_{2\Delta h}),\quad \ldots\Big),\end{aligned} \tag{30}$$

where the error terms $o(\epsilon^d)$ have been omitted as they are set to zero in practical applications. Note that the correction terms in Eq.1 generally depends on all vector elements in $\mathbf{g_{ij,T}}$.

2.10 Computer software and code

The `UF-Software` software is freely available to download (Cornell et al., 2019). The software comprises two main components: the `ModelSimulator` and the `ModelConstructor` which, respectively, can be used to generate STPPs and SCMs from user-defined RCP-process model descriptions. Note that, since MFPMs are a reduced form of SCMs, the `ModelConstructor` can also generate MFPMs. The `ModelSimulator` uses the Gillespie algorithm (Gillespie, 1977) and is written in the programming language C, and the `ModelConstructor` is written in the Wolfram Mathematica software. Instructions on how to download the `UF-Software` are provided in the Supplementary Information (SI.1).

3 Methods and Model

3.1 The model implementation pipeline

For this study, we created a model implementation pipeline that systematises the use of the `UF-Software` in a number of steps (A1, B1-B4, C1-C7, D1 in Figure 1). The pipeline includes model formulation using RCP-processes (A1), the implementation of STPPs (B1-B4) and SCMs (C1-C7), a visual comparison of STPP, SCM and MFPM generated population dynamics (C7), and analysis of SCM and MFPM equations (D1). Note that, as MFPM equations are a reduced form of SCM equations, they are also obtained in the pipeline. Note also that the initial cell configurations (B2, C4) can be generated *in silico* or be obtained from biological data, and that spatial cumulants from point patterns pertaining to both simulation data and biological data can be calculated (B4) and visualised (C3). If suitable for the application, analytical results from (D1) can be used in the model description. Instructions on how to download, run and modify the code files for each pipeline step are provided in the Supplementary Information (SI.1, SI.2).

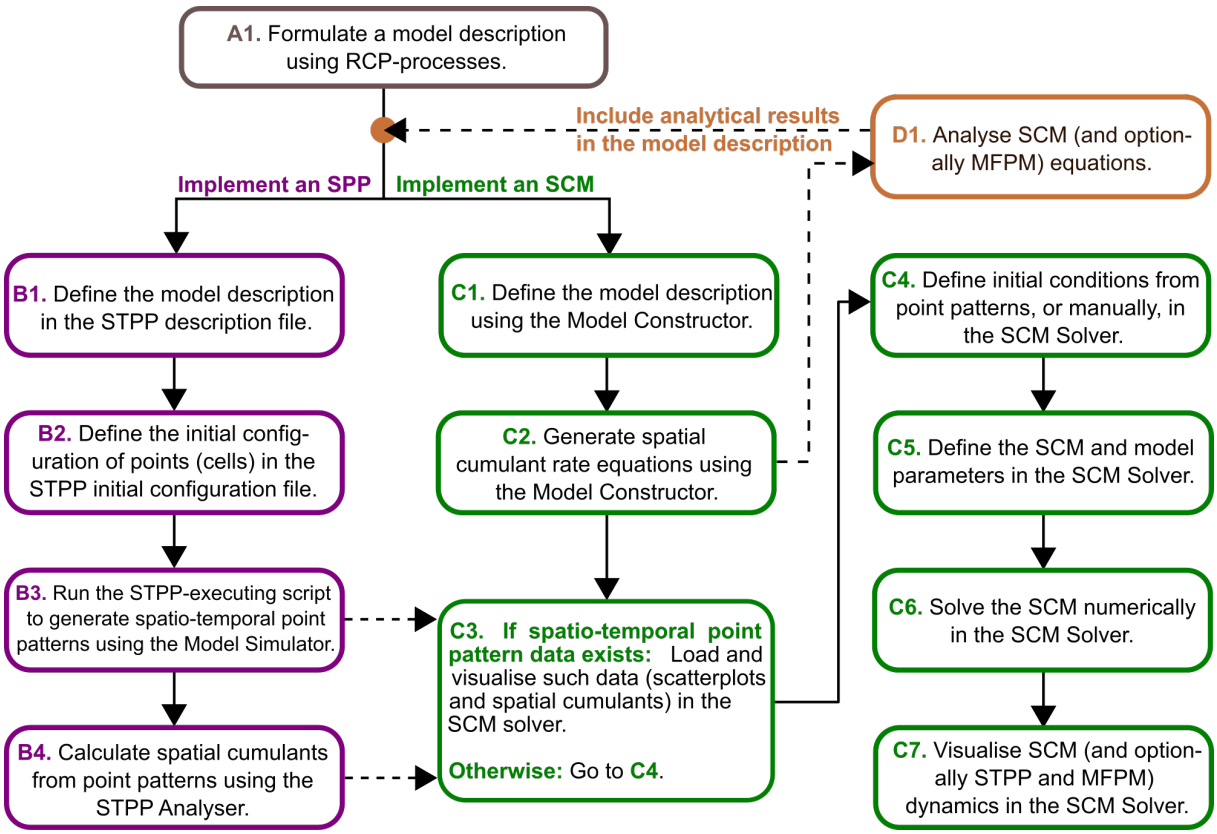

Figure 1: **We developed a pipeline that streamlines the implementation, analysis and output comparison of spatio-temporal point processes (STPPs), mean-field population models (MFPMs) and spatial cumulant models (SCMs).** The figure shows the model implementation pipeline that was developed for this study. The pipeline uses the `UF-Software` (Cornell et al., 2019) to implement STPPs (B1-B4), MFPMs and SCMs (C1-C7) from reactant-catalyst-product (RCP) process model descriptions (A1). Note that, as MFPMs are reduced forms of SCMs, they are also handled in (C1-C7).

3.2 Describing a biological system using RCP-processes

As proof-of-concept, we in this study model a theoretical, biological system that can be described as follows:

"Two types of cancer cells, s_1 and s_2, co-exist. Cells of type s_1 produce growth factors which are both internalised by the producer cell and secreted to the environment. Cells of type s_2 do not produce growth factors and must receive growth factors from s_1 cells in order to proliferate. Both s_1 and s_2 cells can internalise growth factors from (other) s_1 cells but, because s_2 cells waste no energy on growth factor production, they benefit more from growth factor uptake than do s_1 cells. Consequently, s_2 cells have a higher growth factor mediated proliferation rate than do s_1 cells. Similarly, s_1 cells express a higher proliferation rate when they receive growth factors from other cells, compared to when they self-produce growth factors. If drugs are applied to the system, s_1 and s_2 cells die at rates δ_1 and δ_2, respectively."

The ways in which cells can interact (and self-interact via autocrine signalling) through growth factors are pictorially shown in Figure 2(a-c), and the key conceptual difference between modelling STPP, SCM and MFPM interactions is show in Figure 2(d,e). The modelled system can be described using the RCP-processes listed in Table 1.

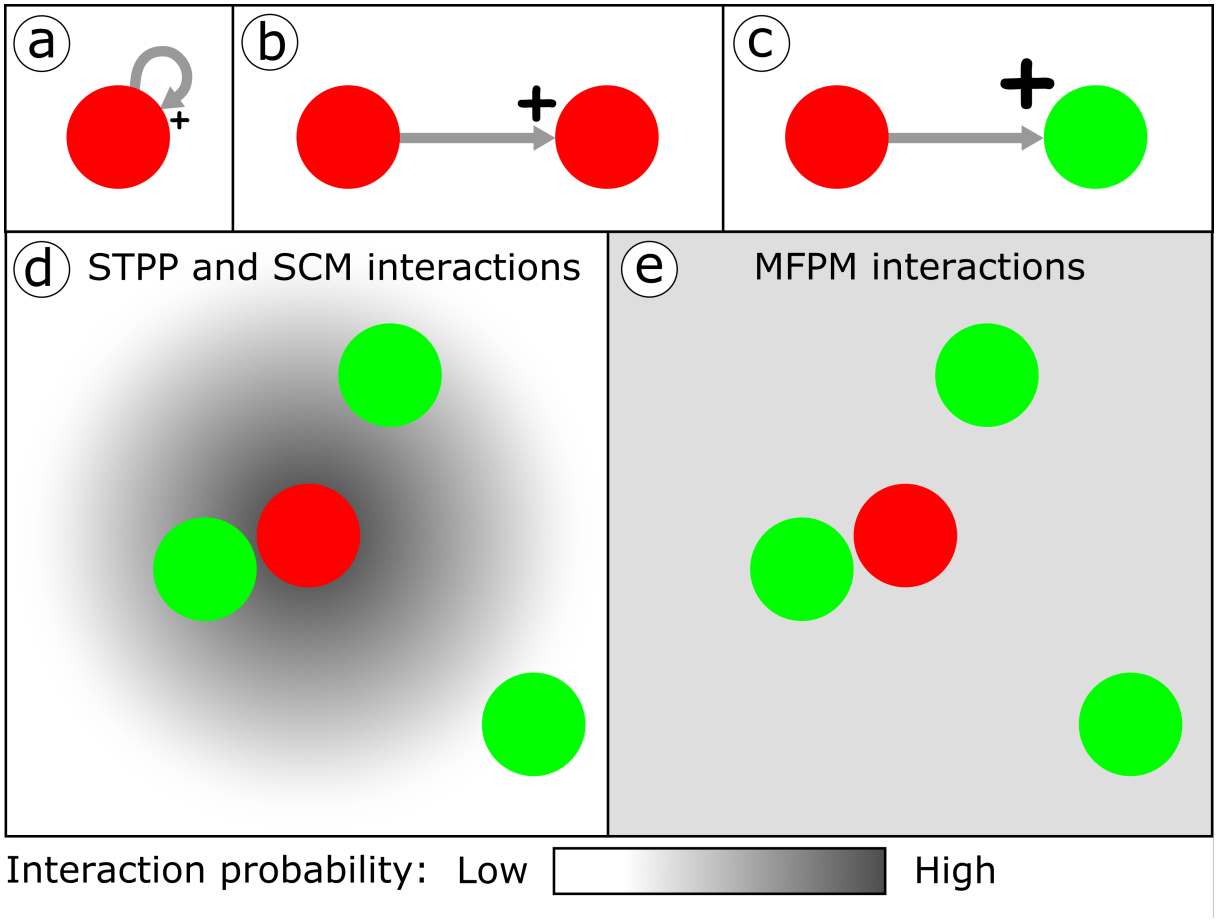

Figure 2: **Cells interact with each other through growth factor secretion and uptake.** Panels (a-c) show the possible ways in which cells in the modelled system can interact (and self-interact via autocrine signalling). The size of the plus (+) mark indicates the benefit (in terms of proliferation rate) that the receiver cell gains from the interaction. (a) Type s_1 cells (red) can produce and internalise their own growth factors. (b) Type s_1 cells can receive growth factors from other s_1 cells. (c) Type s_2 cells (green) can receive growth factors from s_1 cells. Panels (d,e) highlight the difference between modelling interactions in spatio-temporal point processes (STPPs), spatial cumulant models (SCMs) and mean-field population models (MFPMs). These panels show how likely the s_2 cells are to receive growth factors from the focal s_1 cell. In STPPs and SCMs, the probability that such a cell-cell interaction occurs depends on the distance between the two interacting cells, so that cells that are closer to each other are more likely to interact (d). In MFPMs, all cells in the system are equally likely to interact with each other, independently of spatial cell-cell separations (e).

Biological process	Reactants ($\mathbf{r}$), catalysts ($\mathbf{c}$), products ($\mathbf{p}$)	Markov operator	Description
Birth$[s_1, B_1(x_1 - x_2)]$	$\mathbf{r} = \varnothing$, $\mathbf{c} = \{x_1, s_1\}$, $\mathbf{p} = \{x_2, s_1\}$.	$L_B^{s_1}$	A cell with mark s_1 in location x_1 produces a cell of mark s_1 in location x_2 with kernel $B_1(x_1 - x_2)$.
Birth By Facilitation $[s_1, s_1, B_{11}(x_1 - x_2), C(x_1 - x_3)]$	$\mathbf{r} = \varnothing$, $\mathbf{c} = \{\{x_1, s_1\}, \{x_3, s_1\}\}$, $\mathbf{p} = \{x_2, s_1\}$.	$L_{BF}^{s_1 s_1}$	A cell with mark s_1 in location x_1 produces a cell of mark s_1 in location x_2 with kernel $B_{11}(x_1 - x_2)$. This process is facilitated by a cell with mark s_1 in location x_3 with kernel $C(x_1 - x_3)$.
Birth By Facilitation $[s_2, s_1, B_{12}(x_1 - x_2), C(x_1 - x_3)]$	$\mathbf{r} = \varnothing$, $\mathbf{c} = \{\{x_1, s_2\}, \{x_3, s_1\}\}$, $\mathbf{p} = \{x_2, s_2\}$.	$L_{BF}^{s_2 s_1}$	A cell with mark s_2 in location x_1 produces a cell of mark s_2 in location x_2 with kernel $B_{12}(x_1 - x_2)$. This process is facilitated by a cell with mark s_1 in location x_3 with kernel $C(x_1 - x_3)$.
Density Independent Death$[s_1, \delta_1]$	$\mathbf{r} = \{x_1, s_1\}$, $\mathbf{c} = \varnothing$, $\mathbf{p} = \varnothing$.	$L_{DI}^{s_1}$	A cell with mark s_1 in location x_1 dies at rate δ_1.
Density Independent Death$[s_2, \delta_2]$	$\mathbf{r} = \{x_1, s_2\}$, $\mathbf{c} = \varnothing$, $\mathbf{p} = \varnothing$.	$L_{DI}^{s_2}$	A cell with mark s_2 in location x_1 dies at rate δ_2.

Table 1: The table includes the reactant-catalyst-product (RCP) processes that are used to describe the modelled system, in which growth factor producing (s_1) and non-producing (s_2) cells co-exist and can interact with each other.

3.3 Describing a biological system using Markov operators

When no drugs are applied to the system, the model is described by the total Markov operator

$$L = L_B^{s_1} + L_{BF}^{s_1 s_1} + L_{BF}^{s_2 s_1} \ , \tag{31}$$

where all birth kernels have the same Gaussian dispersal shape (*i.e.* the same standard deviations) but different integrals such that

$$b_1 = 2\pi \int_0^\infty B_1(r) r dr < b_{11} = 2\pi \int_0^\infty B_{11}(r) r dr < b_{12} = 2\pi \int_0^\infty B_{12}(r) r dr, \tag{32}$$

for $r = |x_1 - x_2|$, and the total integral of the interaction kernel is

$$c = 2\pi \int_0^\infty C(r) r dr \tag{33}$$

for $r = |x_1 - x_3|$. When drugs are applied, the model's total Markov operator becomes

$$L = L_B^{s_1} + L_{BF}^{s_1 s_1} + L_{BF}^{s_2 s_1} + L_{DI}^{s_1} + L_{DI}^{s_2} \ . \tag{34}$$

In this study, we set the parameter values pertaining to the Markov operators $L_B^{s_1}, L_{BF}^{s_1 s_1}$ and $L_{BF}^{s_2 s_1}$ in step A1 (Figure 1), and thus assume that these parameter values are inherent to the modelled cell population. Conversely, we assume that the parameters δ_1 and δ_2, pertaining to the Markov operators $L_{DI}^{s_1}$ and $L_{DI}^{s_2}$ can be modulated by drug doses. In Section 4.2, we therefore use the MFPM and SCM equations, that were generated by the `UF-Software`, to analytically derive death rates that result in non-growing subpopulations in the MFPM and SCM at the treatment time T (D1, Figure 1). These death rates are then implemented in the STPP, as responses to implicitly modelled drug. All model parameter values are listed in the Supplementary Information (SI.3).

3.4 Describing a biological system using MFPM and SCM equations

By implementing the model described by Eq.34 into the `UF-Software`, we obtain the following system of ODEs,

$$\frac{dq_1(t)}{dt} = H_{q_1} = \underbrace{b_1 q_1(t)}_{\text{from } L_B^{s_1}} + \underbrace{b_{11} c q_1(t)^2}_{\text{from } L_{BF}^{s_1 s_1}} - \underbrace{\delta_1 q_1(t)}_{\text{from } L_{DI}^{s_1}}, \tag{35a}$$

$$\frac{dq_2(t)}{dt} = H_{q_2} = \underbrace{b_{12} c q_1(t) q_2(t)}_{\text{from } L_{BF}^{s_2 s_1}} - \underbrace{\delta_2 q_2(t)}_{\text{from } L_{DI}^{s_2}}, \tag{35b}$$

$$\frac{dp_1(t)}{dt} = H_{p_1} = \underbrace{b_1 p_1(t)}_{\text{from } L_B^{s_1}} + \underbrace{W_{11}(t) + 2b_{11} c q_1(t) p_1(t)}_{\text{from } L_{BF}^{s_1 s_1}} - \underbrace{\delta_1 p_1(t)}_{\text{from } L_{DI}^{s_1}}, \tag{35c}$$

$$\frac{dp_2(t)}{dt} = H_{p_2} = \underbrace{W_{12}(t) + b_{12} c\Big(q_1(t) p_2(t) + q_2(t) p_1(t)\Big)}_{\text{from } L_{BF}^{s_2 s_1}} - \underbrace{\delta_2 p_2(t)}_{\text{from } L_{DI}^{s_1}}, \tag{35d}$$

$$\begin{aligned}\frac{d\tilde{g}_{k,11}(t)}{dt} = H_{g_{11}} &= \underbrace{2\widetilde{B_1}(k)\Big(q_1(t) + \tilde{g}_{k,11}(t)\Big)}_{\text{from } L_B^{s_1}} + \underbrace{2\widetilde{B_{11}}(k) q_1(t)\Big(c + \widetilde{C}(k)\Big)\Big(q_1(t) + \tilde{g}_{k,11}(t)\Big)}_{\text{from } L_{BF}^{s_1 s_1}} \\ &- \underbrace{2\delta_1 \tilde{g}_{k,11}(t)}_{\text{from } L_{DI}^{s_1}},\end{aligned} \tag{35e}$$

$$\begin{aligned}\frac{d\tilde{g}_{k,12}(t)}{dt} = H_{g_{12}} &= \underbrace{\widetilde{B_1}(k)\tilde{g}_{k,12}(t)}_{\text{from } L_B^{s_1}} + \underbrace{\widetilde{B_{11}}(k) q_1(t)\tilde{g}_{k,12}(t)\Big(c + \widetilde{C}(k)\Big)}_{\text{from } L_{BF}^{s_1 s_1}} \\ &+ \underbrace{\widetilde{B_{12}}(k)\Big(c q_1(t)\tilde{g}_{k,12}(t) + \widetilde{C}(k) q_2(t)(q_1(t) + \tilde{g}_{k,11}(t))\Big)}_{\text{from } L_{BF}^{s_1 s_2}} - \underbrace{\delta_1 \tilde{g}_{k,12}(t)}_{\text{from } L_{DI}^{s_1}} - \underbrace{\delta_2 \tilde{g}_{k,12}(t)}_{\text{from } L_{DI}^{s_2}},\end{aligned} \tag{35f}$$

$$\frac{d\tilde{g}_{k,22}(t)}{dt} = H_{g_{22}} = \underbrace{2\widetilde{B_{12}}(k)\Big(c q_1(t)(q_2(t) + \tilde{g}_{k,22}(t)) + \widetilde{C}(k) q_2(t)\tilde{g}_{k,12}(t)\Big)}_{\text{from } L_{BF}^{s_2 s_1}} - \underbrace{2\delta_2 \tilde{g}_{k,22}(t)}_{\text{from } L_{DI}^{s_2}}, \tag{35g}$$

where $\tilde{\cdot}$ denotes the Fourier transform of $\cdot$, and k is the independent variable (the spatial frequency) in Fourier space. The k-subscripts have been introduced to denote the $\tilde{g}$-variables dependence on k and

$$W_{11}(t) = 2\pi b_{11} \int_0^\infty k\tilde{g}_{k,11}(t)\widetilde{C}(k)dk, \tag{36a}$$

$$W_{12}(t) = 2\pi b_{12} \int_0^\infty k\tilde{g}_{k,12}(t)\widetilde{C}(k)dk. \tag{36b}$$

In the absence of drugs, terms resulting from the operators $L_{DI}^{s_1}$ and $L_{DI}^{s_2}$ can be omitted, or, equivalently, δ_1 and δ_2 can be set to zero. The SCM is described by Eqs.35(a-g) and Eqs.36(a,b), whereas the MFPM is described by Eqs.35(a,b) only.

3.5 Initial cell configurations and initial conditions

In this study, we consider three different initial cell configurations (ICCs). The ICCs have the same first order spatial cumulants, but different second order spatial cumulants (Figure 3). In ICC.1, cells of type s_1 and s_2 are uniformly, randomly distributed across the simulated domain D. In ICC.2, cells of type s_2 are uniformly, randomly distributed across D, whereas type s_1 cells are randomly distributed within clusters. In ICC.3, both type s_1 and s_2 cells are clustered. In order to set the initial conditions for the SCM and MFPM models, we calculate densities and spatial covariances from the point patterns for all $i, j = 1, 2$, these calculations are used to set $q_i(t = 0)$ and $\mathbf{g_{ij}}(t = 0)$. This procedure is outlined in the Supplementary Information (SI.2). The initial values for the corrections are set to zero, so that $p_i(t = 0) = 0$, for $i = 1, 2$.

4 Results

4.1 SCMs capture STPP-generated cell population dynamics

We first set out to model the no-drug scenario with ICCs 1,2 and 3. To do this, we first implement the STPP (Eq. 31) to generate 100 spatio-temporal point patterns from each ICC. We thereafter solve the MFPM (35(a,b)) and SCM (35(a-g) with 36(a-b)) equations numerically, using initial conditions for the spatial cumulants measured at the respective ICCs. In this proof-of-concept study, we will qualitatively say that a deterministic model "captures STPP dynamics", if the model's predicted spatial cumulants lie within the minimum and maximum spatial cumulant values of 100 STPP-generated spatio-temporal point patterns.

Our results demonstrate that MFPM and SCM density dynamics coincide for ICC.1 only. For the simulated time duration, the MFPM is able to capture STPP-generated density dynamics resulting from ICC.1, where all cells are uniformly randomly distributed, but fail to do so for ICCs 2 and 3 (Figure 3). As the cell-cell interactions via growth factors become more regional on the simulated domain, due to cell clustering, the MFPM performs worse in terms of describing STPP dynamics. This can be visually appreciated in Figure 3, in which the deviation between MFPM and STPP dynamics increases for lower rows in the figure. On the other hand, the spatially informed SCM is able to capture STPP-generated density dynamics resulting from all considered ICCs in the simulated time duration (Figure 3). This is due to the fact that SCMs account for spatio-temporal cell population structures by including equations that describe how the spatial covariances evolve in time. Indeed, our results show that spatial covariances calculated by SCMs capture those generated by STPPs (Figure 4). In summary, the results in Figures 3 and 4 show that SCMs can capture STPP-generated cell population dynamics, even when MFPMs fail to do so.

4.2 SCM-informed treatment strategies outperform MFPM-informed treatment strategies in STPP-generated cell populations

We next set out to derive theoretical drug doses (here implicitly modelled via cell death rates) that stop both subpopulations from growing. In other words, we want to find the model parameters δ_1 and δ_2 that cause the derivatives describing population growths to be zero at the treatment time T. We thus derive MFPM-informed drug doses by setting

$$H_{q_1}(T) := 0, \tag{37a}$$

$$H_{q_2}(T) := 0. \tag{37b}$$

Solving Eqs.37(a,b) for δ_1^{MFPM} and δ_2^{MFPM}, where the superscripts denote that these are the MFPM-informed doses, yields

$$\delta_1^{\mathrm{MFPM}} = b_1 + b_{11} c\, \hat{u}_{1,T}^{(1)}, \tag{38a}$$

$$\delta_2^{\mathrm{MFPM}} = b_{12} c\, \hat{u}_{1,T}^{(1)}. \tag{38b}$$

Here, the hat-notation ($\hat{\cdot}$) has been introduced to denote quantities that will be measured from point patterns, and the variables $q_i(t)$ have been substituted with $\hat{u}_{i,T}^{(1)}$, *i.e.* the measured density of subpopulation i at time T. Similarly, we derive SCM-informed drug by setting

$$H_{q_1}(T) + \epsilon^2 H_{p_1}(T) := 0, \tag{39a}$$

$$H_{q_2}(T) + \epsilon^2 H_{p_2}(T) := 0, \tag{39b}$$

and solving for δ_1^{SCM} and δ_2^{SCM} with all correction terms p_i set to zero upon measuring the densities and spatial covariances. Since all model parameters and variables are positive at time T, this yields

$$\delta_1^{\mathrm{SCM}} = \frac{b_1 \hat{u}_{1,T}^{(1)} + b_{11} c \cdot (\hat{u}_{1,T}^{(1)})^2 + \epsilon^2 \hat{W}_{11,T}}{\hat{u}_{1,T}^{(1)}}, \tag{40a}$$

$$\delta_2^{\mathrm{SCM}} = \frac{b_{12} c\, \hat{u}_{1,T}^{(1)} \hat{u}_{2,T}^{(1)} + \epsilon^2 \hat{W}_{12,T}}{\hat{u}_{2,T}^{(1)}}, \tag{40b}$$

To test these drug doses in the STPP, we, for each spatio-temporal point-pattern, measure the quantities $\hat{u}_{1,T}^{(1)}, \hat{u}_{2,T}^{(1)}, \hat{W}_{11,T}, \hat{W}_{12,T}$ at the treatment time and calculate the MFPM and SCM-informed doses. Note

that the quantities $\widehat{W}_{11,T}$ and $\widehat{W}_{12,T}$ incorporate the spatial structure of the regarded cell population (via spatial covariances) and local effects of growth factor cell-cell interactions (via the kernel $C(r)$). After time T, we then let each spatio-temporal point pattern progress further in time with its individual death rates δ_1 and δ_2 applied to the STPP (Eq.34).

Our results show that both MFPM and SCM-informed treatment doses are able to stop subpopulations s_1 and s_2 from increasing for cell populations that started at ICC.1 (Figure 5 top row). However, for populations that started with ICC.2, the SCM-informed doses drastically outperform MFPM-informed doses in terms of inhibiting population growths (Figure 5 middle row). In this case, the MFPM-informed doses underestimate the required values of δ_1 and δ_2 due to the synergistic growth effects that arise from cell type $s_1 - s_1$ proximity, and cell type s_2 being close enough to s_1 cells to benefit from their secreted growth factors. In cell populations initiated with ICC.3, type s_1 cells are benefiting from being close to each other, whereas type s_2 cells are too far away the from s_1 cells to benefit from high s_1 densities. Accordingly, the MFPM-informed doses adequately inhibit population growths for s_2 but not for s_1 (Figure 5 bottom row). However, the SCM-informed doses inhibit both s_1 and s_2 population growths for ICC.3. In conclusion, SCMs enable the derivation of treatment strategies that are informed by (1) the spatial structure of the targeted cell population and (2) by localised cell-cell interactions. In our theoretical study, and in terms of inhibiting subpopulation growths, SCM-informed doses match MFPM-informed doses for ICC.1, and outperform MFPM-informed doses for ICCs 2 and 3.

5 Discussion

Most current cancer treatments target genomic aberrations without consideration for eco-evolutionary tumour aspects that change over the course of treatment, such as cell-cell and cell-microenvironment interactions. The lack of understanding of such dynamical tumour aspects is one factor that may be hindering the development of efficient targeted treatment protocols (Gatenby et al., 2020; Wang and Deisboeck, 2019). However, clinical trials that are informed by mathematical modelling and take dynamical tumour processes into account have started to emerge (Zhang et al., 2017; Poels et al., 2021).

Although not applied in clinical settings, IBMs are widely used in mathematical oncology to study cancer eco-evolution in response to cell-cell interactions and treatments. The appeal of IBMs has increased with the resolution of state-of-the-art experimental and clinical cancer data revealing information on the single-cell level. With their spatio-temporal structure, IBMs, unlike MFPMs, have the ability to include both spatial information about how subpopulations are located in tumours (from spatial transcriptomics (Hunter et al., 2021)) and temporal information about how genetic alterations in tumour cell subpopulations propagate over generations to evade treatments (from phylogenetic analysis (Schwartz and Schäffer, 2017)). However, without an analytical mathematical framework in which to analyse IBMs, it is difficult to describe relationships between model variables and model parameters in a mechanistic way that lets us perturb the modeled system and better understand its inter-component dependencies. In the context of cancer, theoreticians, experimentalists and clinicians may be interested in perturbing cancer systems onto evolutionary trajectories that are favourable from treatment perspectives. Analytical mathematical models that account for treatment effects and cell-cell interactions can provide instructions for how to do so (Zhang et al., 2017; Kaznatcheev et al., 2019).

In this article, we demonstrated that SCMs enable spatially informed treatment strategies and analysis of local interactions in cancer systems. Although the theoretical, biological system that we modelled in this study was of a simple structure, only comprising five RCP-processes, the model could be expanded to include more biological processes. It is straight-forward to use the `UF-Software` to implement processes such as density-dependent cell death, cell motility and cell-type conversion via cell-intrinsic or external factors. We also note that SCMs could be further improved to include more functionalities that would be relevant in cell biology. For example, in this study, we categorised cells with discrete marks, so that each cell belonged to one of two subpopulations with set traits. However, in many cell biology scenarios, it would be more relevant to use continuous marks to describe *e.g.* growth factor production, cell motility, drug resistance and gene-expression in other forms. Moreover, in this study, all model parameters were cell-intrinsic constants. In order to allow for non-linear effects between a cell's proximity to other cells and its behaviour, the model parameters could be adjusted to be functions of *e.g.* time, space or continuous marks. We leave these suggested improvements to SCMs as future challenges. Another future challenge will be to develop methods to parameterise the SCMs with experimental and, ultimately, clinical data.

We emphasise that even though the mathematical theory that underlies SCMs may appear mathematically challenging at first sight, implementing SCMs (using the `UF-Software` and the pipeline codes developed for this paper) is not. In order to make the methods discussed in this article accessible to the research community, we have provided clear instructions for how to use the pipeline code files in the Supplementary Information (SI.2).

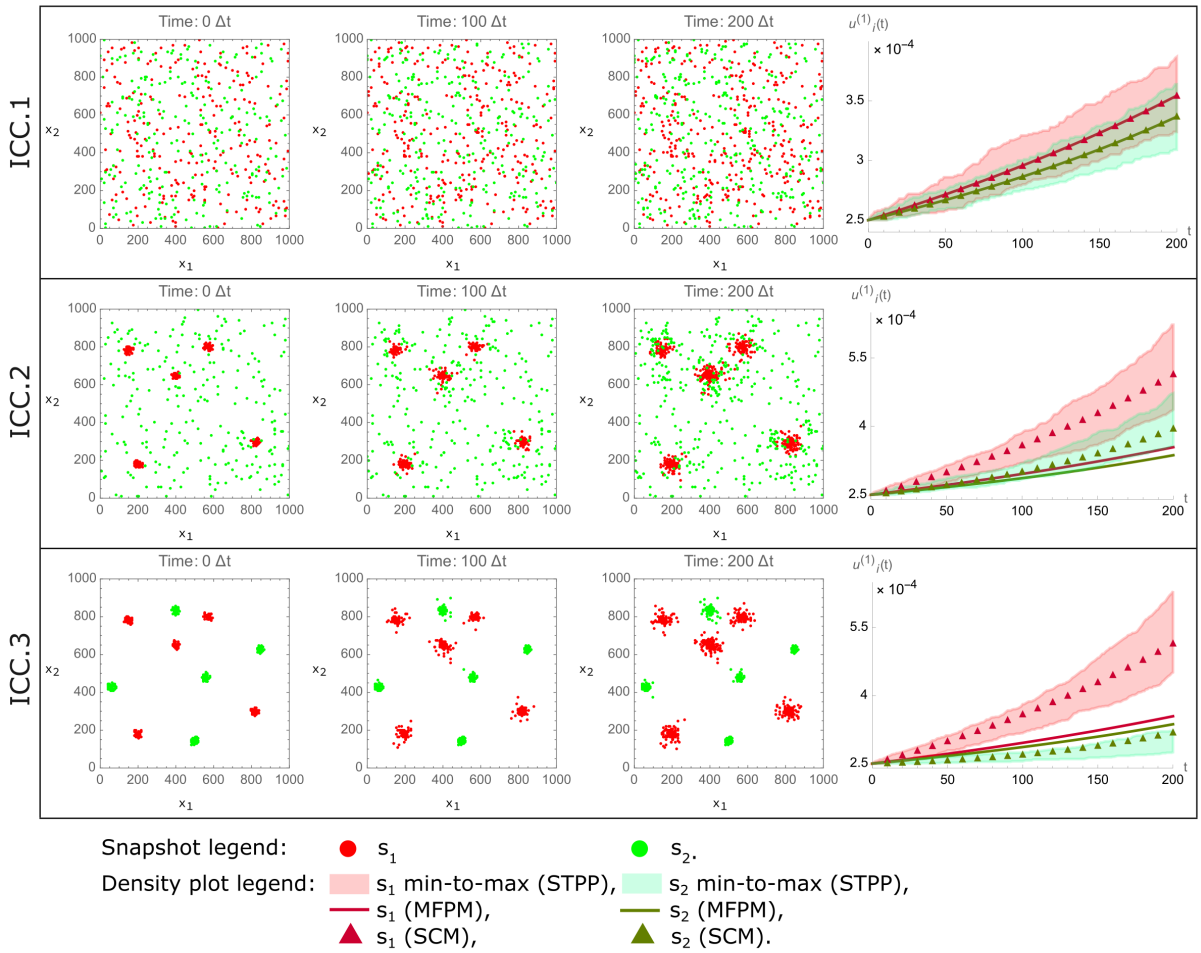

Figure 3: **Spatial cumulant models (SCMs) capture density dynamics generated by spatio-temporal point processes (STPPs), even when mean-field population models (MFPMs) fail to do so.** The figure shows STPP, MFPM and SCM generated cell population dynamics, where each row corresponds to a unique ICC (left-most column). Snapshots from one STPP-generated spatio-temporal point pattern per ICC are shown at time points 0, 100 and 200 Δt. Growth factor producing cells (type s_1) are shown in red, and non-producers (type s_2) are shown in green. The right-most column shows STPP, MFPM and SCM generated density dynamics. In the density plots, the shaded STPP data shows a span of minimum to maximum (min-to-max) density values calculated from 100 spatio-temporal point patterns resulting from the same ICC. MFPM (solid lines) and SCM (triangles) results are obtained by numerically solving the MFPM and SCM equations with initial conditions calculated from the shown ICCs.

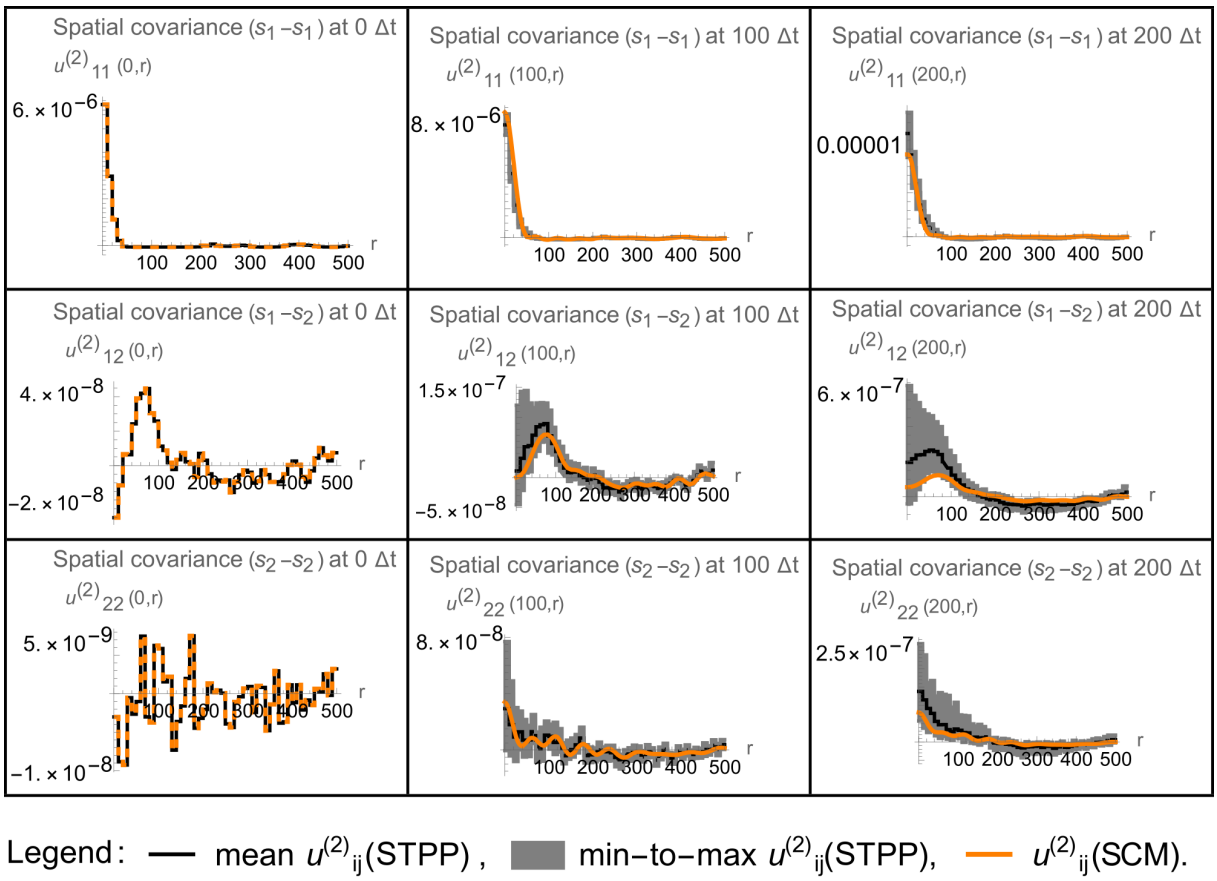

Figure 4: **Spatial cumulant models (SCMs) capture spatial covariance dynamics generated by spatio-temporal point processes (STPPs).** The figure shows STPP and SCM generated spatial covariance dynamics resulting from ICC.2 (as shown in Figure 3). Each row corresponds to a unique pairing of cell types, and each column corresponds to a time point (0, 100 or 200 Δt). Mean and minimum-to-maximum (min-to-max) values from 100 STPP-generated spatio-temporal point patterns are, respectively, shown with solid black lines and shaded gray bands. SCM results (orange) in the two right-most columns are obtained by numerically solving the SCM equations, with the spatial covariances shown in the left-most column as initial conditions.

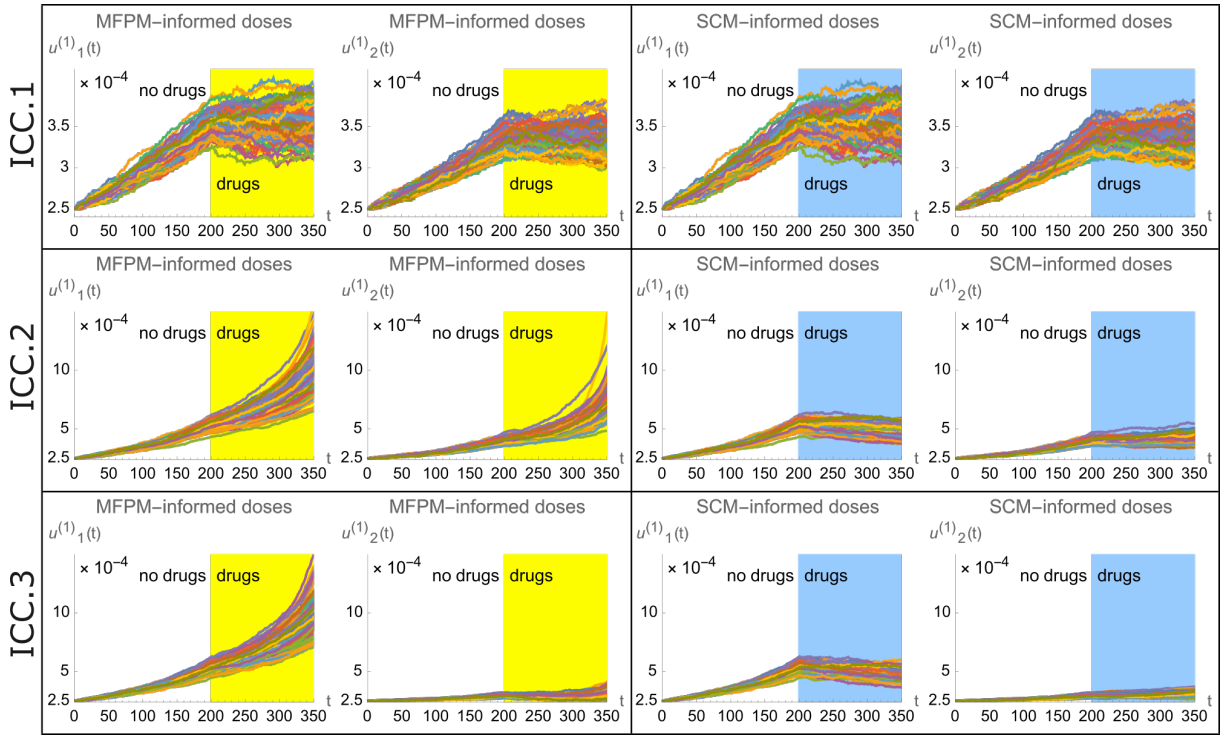

Figure 5: **Treatment strategies informed by spatial cumulant models (SCMs) outperform treatment strategies informed by mean-field population models (MFPMs) in terms of inhibiting population growths in cell populations generated by spatio-temporal point processes (STPPs).** The figure shows STPP-generated density dynamics when drugs are applied at $t = 200\Delta t$. Each row corresponds to the dynamics resulting from a unique ICC (as shown in Figure 3). Each panel includes two plots, one of which shows the density dynamics of the growth factor producing cells ($u_1^{(1)}(t)$), and one of which shows the density dynamics of the non-producer cells ($u_2^{(1)}(t)$). All plots show density dynamics from 100 spatio-temporal point patterns. Every spatio-temporal point pattern is assigned point pattern-specific drug doses (cell death rates) at $t = 200\Delta t$, and is visualised with an individual line. Dynamics resulting from MFPM-informed drug doses (indicated by yellow areas) and SCM-informed drug doses (indicated by blue areas) are respectively shown in the left and right panels.

Multiple research groups have mathematically modelled the effect that growth factor mediated cell-cell interactions have on cancer progression and treatment outcomes. Notably, Zhang *et al.* are using an EGT model to inform treatment strategies in a clinical prostate cancer trial (2017). Their model predicts personalised treatment outcomes in response to drug schedules and assumed interactions amongst testosterone producing, dependent and independent cells. Kaznatcheev *et al.* used an EGT model to show that both drugs and cancer associated fibroblasts modulate cell-cell interactions in co-cultures of drug sensitive and resistant non-small cell lung cancer cells (2019). Haridas *et al.* used a PDE model to quantify how interactions between melanoma cells and fibroblasts effect the spreading of cells in *in vitro* co-cultures, finding no conclusive evidence of any cell-cell interactions via diffusible substrates (2017). Gerlee *et al.* used an IBM and an IBM-derived ODE model to demonstrate that autocrine signaling suffices to cause strong and weak Allee effects in cancer, in line with experimental observations from patient-derived brain tumor cell lines (2022).

We argue that SCMs provide a framework in which to study similar cancer research problems, with the added benefit of easy-to-produce duality: via the `UF-Software`, it is straight-forward to generate both simulations and analytical expressions describing user-defined biological systems. SCMs and the `UF-Software` can be especially helpful in studies when the locality of cell-cell interactions via diffusible factors and resource competition can not be neglected. Moreover, we remark that there exists parallels between the SCM and EGT frameworks, which both are centered around interactions amongst individuals, and we theorise that the SCM methodology of incorporating space may facilitate the derivation of corrected, spatially resolved EGT replicator equations. One important contrast between EGT models and SCMs, however, lies in how the modelled interactions are described. In EGT models, the behaviour of cell populations in response to cell-cell interactions is modelled without any mechanistic descriptions of the interactions (Farrokhian et al., 2022). On the other hand, SCMs build upon rule-based descriptions of how the individuals (cells) in the modelled system act and interact. SCMs can therefore be used to define ensembles of allowable biological mechanisms which could be tested *in vitro*, in line with a bottom-up modelling approach (Hamis et al., 2019). We also anticipate that the opportunity to analytically derive spatially informed cancer treatment strategies, as enabled via SCMs, will inspire new theoretical and applied research ventures.

Code access

Instructions on how to access, run and modify the code files used in this study are available in the Supplementary Information (SI.1, SI.2).

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