Estimating compartment size for stochastic simulations of structured populations

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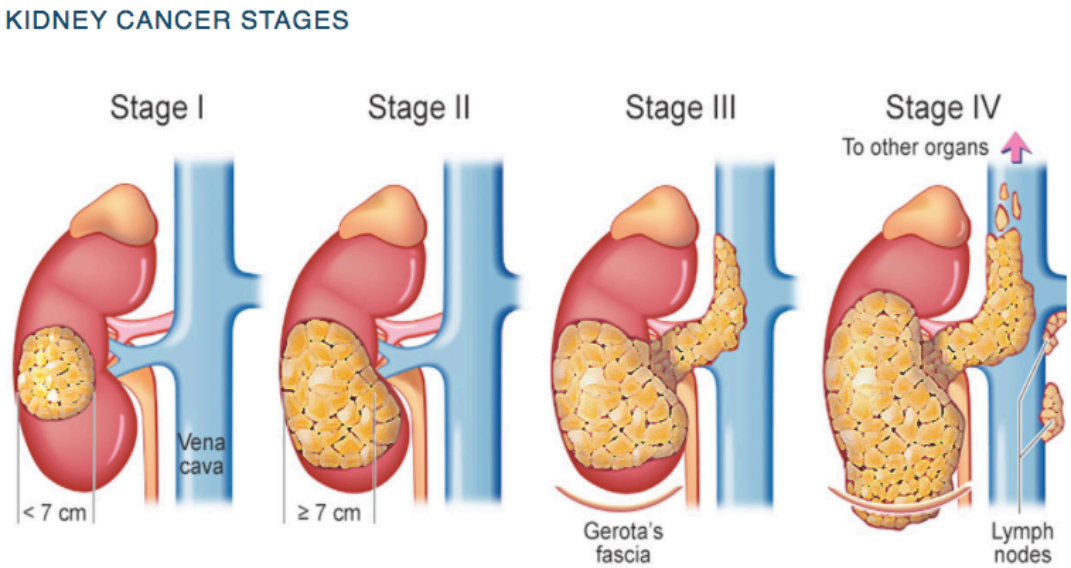
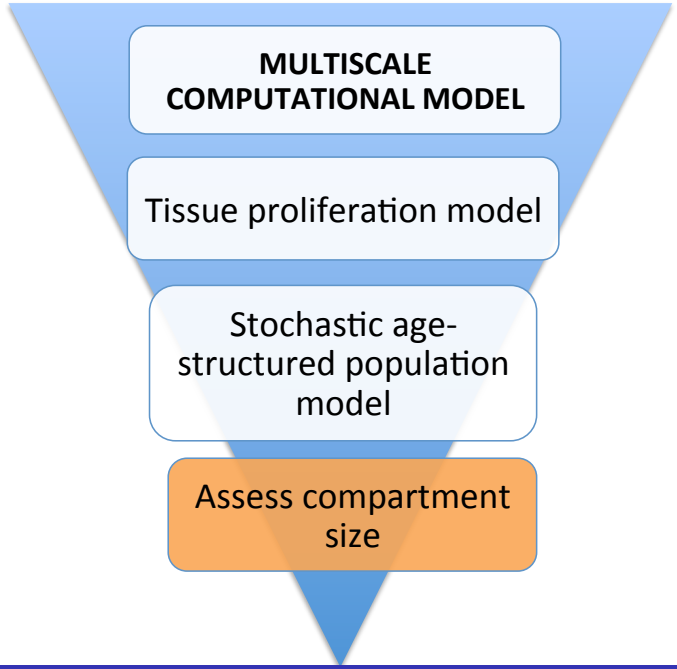
A multiscale model for kidney cancer



(Picture authorship: Bala Sundaram)

- One of the most prone cancers to develop angiogenesis
- Kidney tumors may grow slowy and not pose an inmediate threat
- Surgery vs surveillance dilemma



Stochasticity in biological systems

It is widely recognized that **stochastic effects** play an important role in many biological systems (e.g. due to low copy numbers).

Stochastic analysis and simulation of a chemical system is usually done through the *Chemical Master Equation:*

$$\frac{dP(x,t|x_0,t_0)}{dt} = \sum_{j=1}^{M} \left\{ a_j(x-\nu_j)P(x-\nu_j,t|x_0,t_0) - a_j(x)P(x,t|x_0,t_0) \right\},$$

with propensity functions $\mathbf{a_j}(\mathbf{x})$ defined by

$$P(\text{event j taking place in } [t,t+\delta t)\,|x,t) = \mathbf{a_j}(\mathbf{x})\,\delta t + o(\delta t)\,.$$

Propensity functions and well-mixed systems

Standard propensities in a voxel $V = [0, h]^d$ scale as:

$$a_j(x_1) \propto x_1, \qquad a_j(x_1, x_2) \propto \frac{x_1\, x_2}{h^d}$$

The derivation of specific formulas for propensities of bimolecular (and higher order kinetics as well) demand the system to be **well-mixed**:

"A randomly selected reactant molecule should no more likely be found in any one subvolume of the system than in any other subvolume of the same size".

(Gillespie, Hellander, Petzold, J. Chem. Phys. 2013)

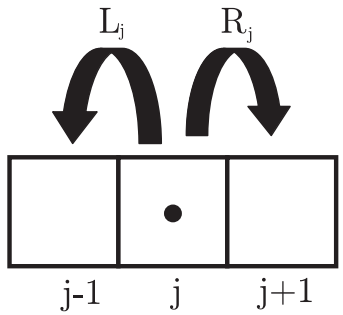
Spatially distributed systems

Many situations require relaxing the assumption of a well-mixed reaction volume.

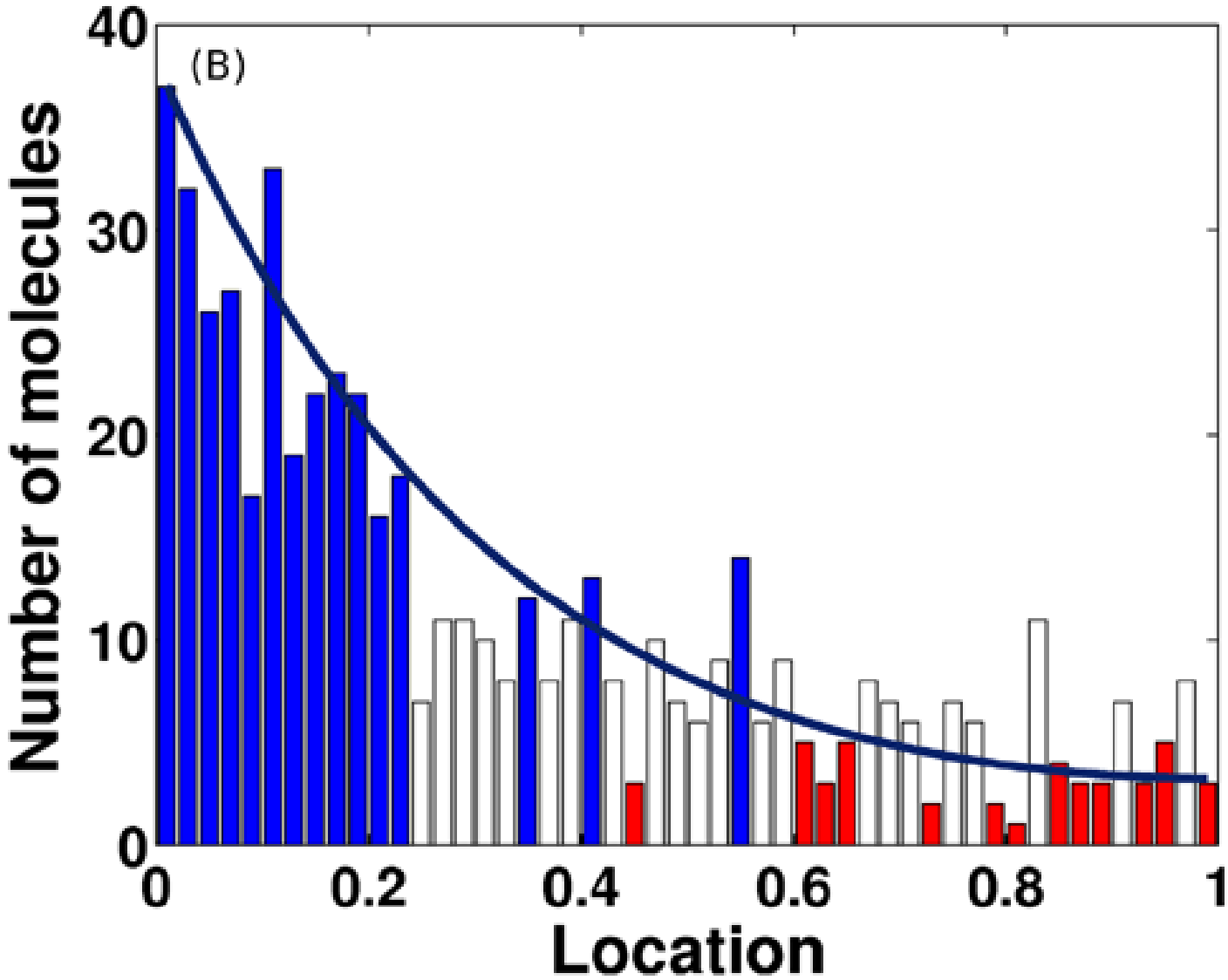
Standard approach for spatially distributed systems

Use compartmentalized models of the system for which each compartment is small enough so that the system can be considered well-mixed within each of them.

Reaction-Diffusion Master Equation. The domain containing the mixture can be discretized into spatially uniform compartments. Diffusion is treated as a jump process between compartments, propensities scaling as h^{-2}.



(Picture authorship: Belmonte-Beitia, Wooley, Scott, Maini, Gaffney)



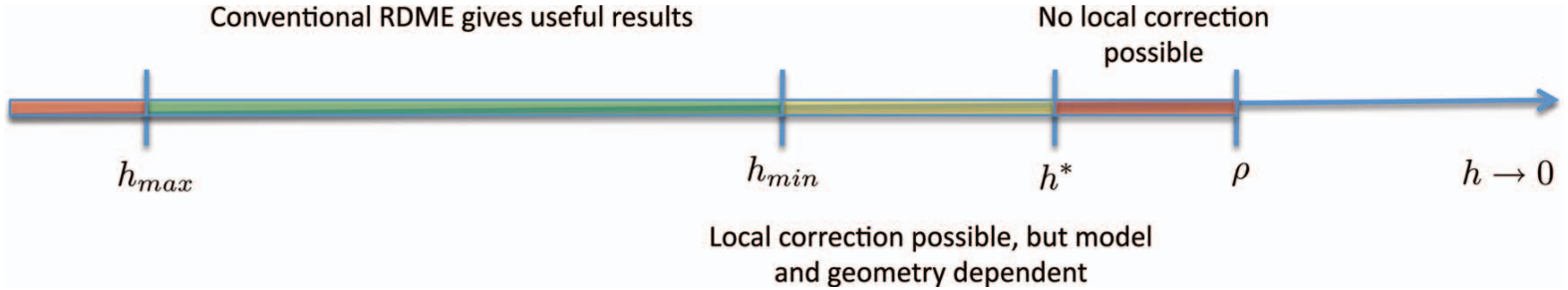
(Picture authorship: Kang, Zheng, Othmer)

How to choose a suitable compartment size *h*?

Ensure that all mobile species within the compartment can transverse it in the time scale of the fastest reaction -in this way the compartment can be considered spatially uniform.

This problem is relevant even for zero- and first-order kinetics:

- Particle number fluctuations increase with decreasing compartment size. (e.g. Gadgil, Lee, Othmer, Bull. Math. Biol. 2005)
- It is crucial to control the crossover in *h* from the diffusion-dominated to the reaction-dominated regime. Too small compartments $\Rightarrow$ diffusion events dominate.



(Picture authorship: A. Hellander, S. Hellander, L. Petzold, D. Gillespie)

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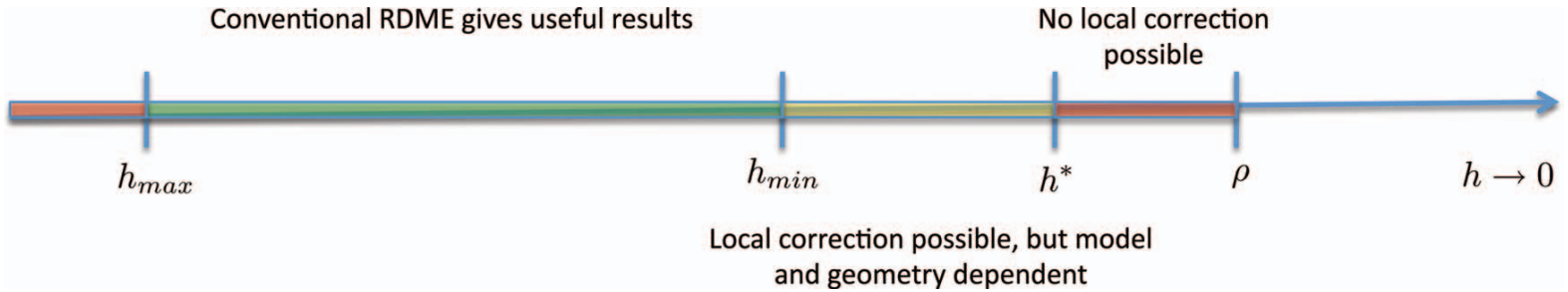
Ensure that all mobile species within the compartment can transverse it in the time scale of the fastest reaction -in this way the compartment can be considered spatially uniform.

Warning: The Reaction-Diffusion Master Equation is not convergent in the limit $h \to 0$ for spatial dimension $d \geq 2$ if second-order kinetics are present.

(Isaacson, SIAM J. Appl. Math. 2009; Hellander, Hellander, Petzold, Phys.Rev. E 2012)



(Picture authorship: A. Hellander, S. Hellander, L. Petzold, D. Gillespie)

How to choose a suitable compartment size h?

A number of criteria have been proposed along the former lines; they usually amount to have

$$\text{diffusion timescale} \ll \text{reaction timescale}$$

(Bernstein, Isaacson–Peskin, Erban–Chapman,...)

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"Another aspect inadequately addressed in previously-cited work is the effect of compartment size on the magnitude of the stochastic fluctuations, as measured by the coefficient of variation of solutions."

(Kang, Zheng, Othmer, J. Math. Biol. 2012)

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Kang–Zheng–Othmer introduce:

1. a measure based on the stabilization of a generalized coefficient of variation.
2. a criterion based on convergence to a uniform state (stationary or time-dependent) for the mean field model.

These two were shown to agree remarkably well.

Deterministic reaction-diffusion systems

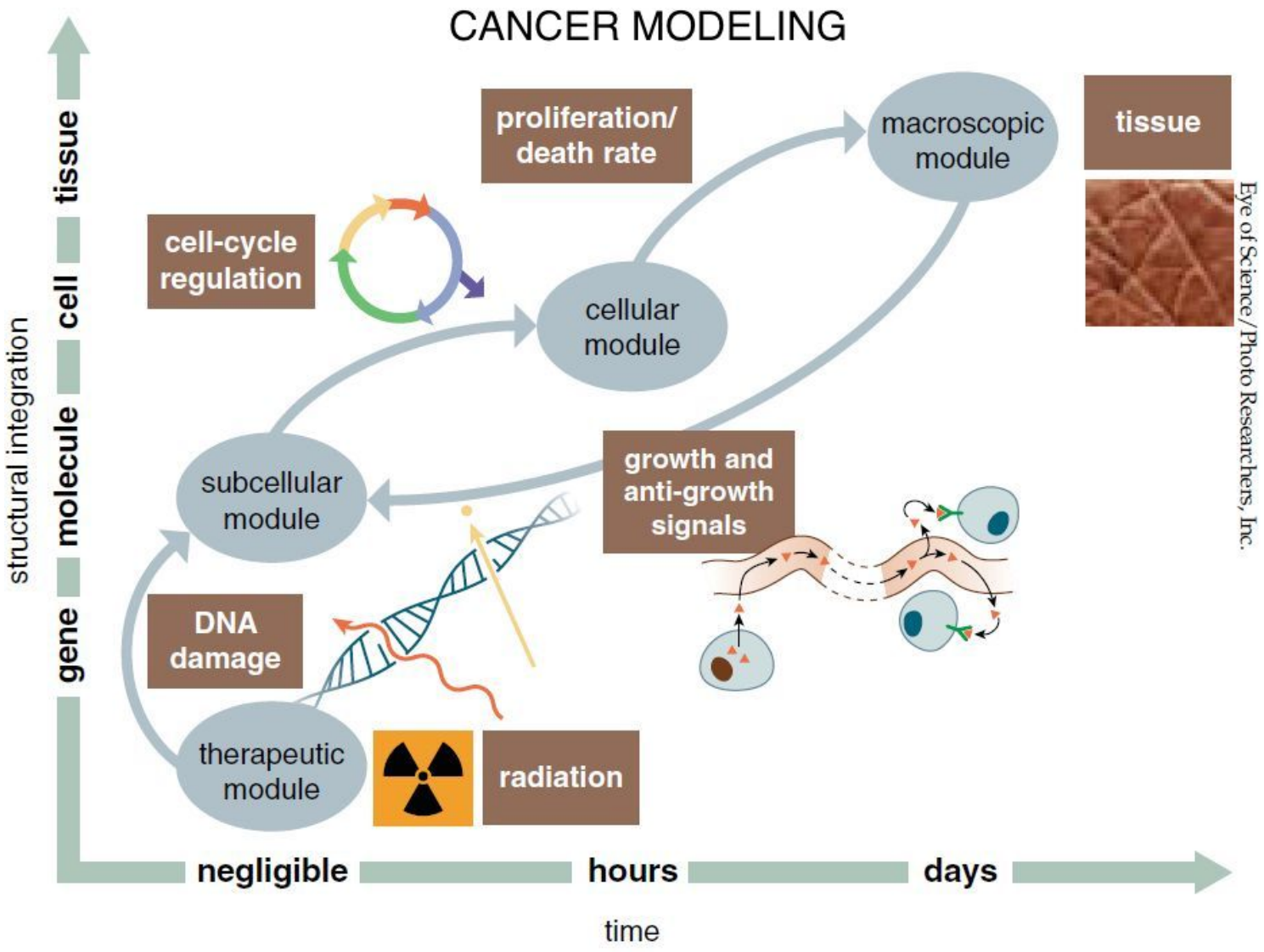
The (well-mixedness) criterion by Kang–Zheng–Othmer based on convergence to a uniform state at the level of the mean field equations gives an **upper bound** for h.

This generalizes previous results by Ashkenazi–Othmer and Conway–Hoff–Smoller on the (exponential) convergence *to uniform states* for systems of reaction-diffusion equations.

Relative entropy methods: recent results showing exponential convergence *to equilibrium* for reaction-diffusion systems arising from complex balanced chemical reaction networks.

(e.g. Desvillettes, Fellner, Tang, SIAM J. Math. Anal. 2017; Fellner, Tang, Z. Angew. Math. Phys. 2018)

What about (age-)structured models?



Dynamics of an age-structured population

Intracellular scale:

Replication events, cell cycle model.

- Input: oxygen concentration.
- Output: replication age.

Resource scale:

Reaction–diffusion equation for oxygen concentration.

- Oxygen is consumed by the population.

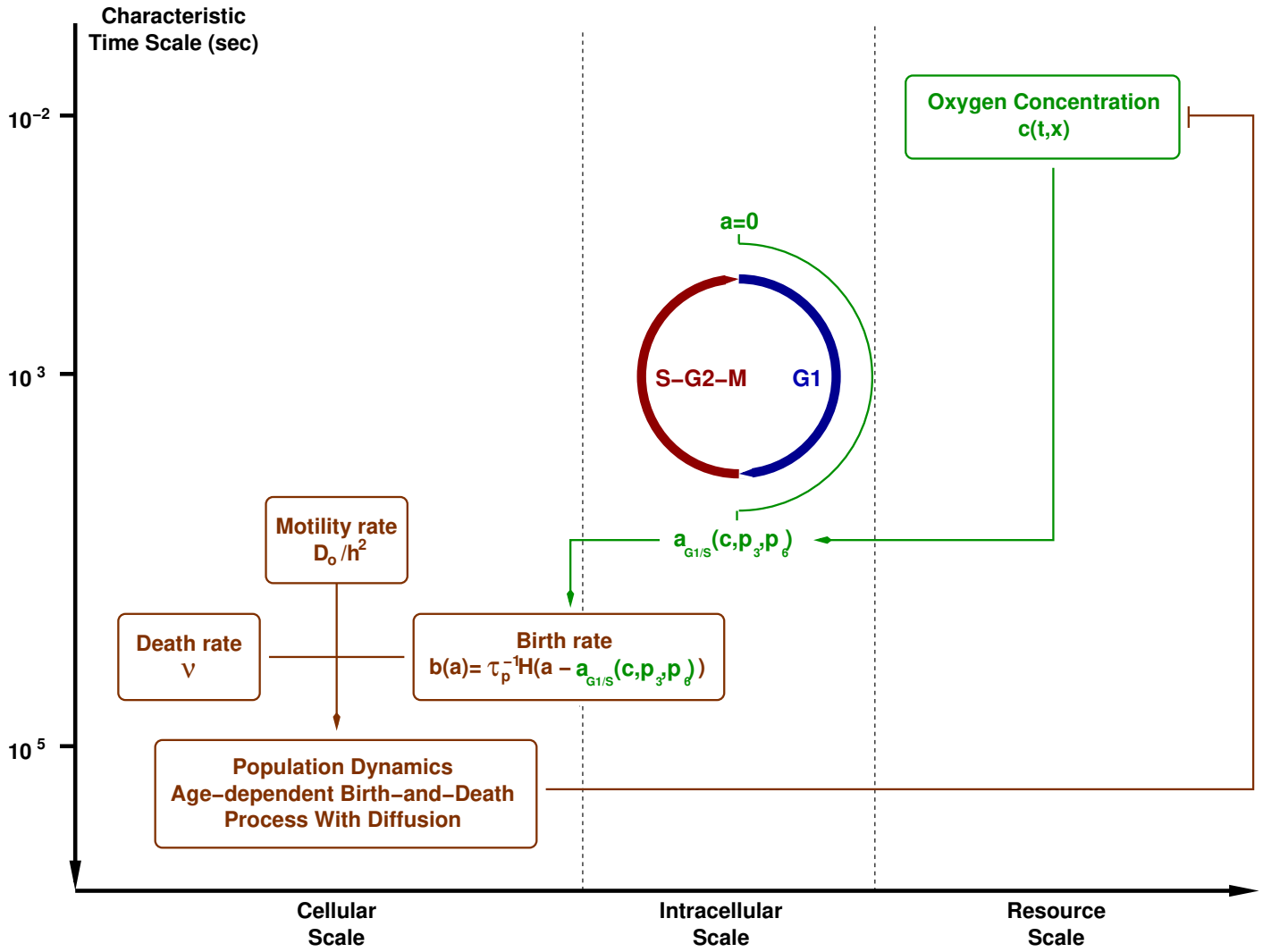
Cellular scale:

Age-dependent birth-death-diffusion process.

- Birth events depend on the cell cycle model.

(de la Cruz, Guerrero, Calvo, Alarcón, J. Comp. Phys. 2017)

Dynamics of an age-structured population



(de la Cruz, Guerrero, Calvo, Alarcón, J. Comp. Phys. 2017)

Dynamics of an age-structured population

- Birth rates $b(a) = \tau_p^{-1} H(a - a_{G1\setminus S}(c))$
- Death rates ν
- Diffusion rates D_n/h^2.

Mean field model for population $n(t, a, x)$ and oxygen $c(t, x)$ densities:

$$\begin{aligned} \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= D_n \frac{\partial^2 n}{\partial x^2} - (b(a) + \nu)\, n \\ n(t, a = 0, x) &= 2 \int_0^\infty b(a)\, n(t, a, x)\, da \\ \frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} - k\, c \int_0^\infty n(t, a, x)\, da + S(t, x) - k_2 c \end{aligned}$$

(de la Cruz, Guerrero, Calvo, Alarcón, J. Comp. Phys. 2017)

Homogeneization result

Compartment size determination criterion: the population should converge to a spatially-uniform solution (fast enough) at the level of the mean field model.

We study the complete model for $x \in [0, h]$ with homogeneous source term $S > 0$ and spatial boundary conditions

$$\partial_x n(t, a, x = 0) = \partial_x n(t, a, x = h) = 0 \,,$$

$$\partial_x c(t, x = 0) = \partial_x c(t, x = h) = 0 \,.$$

Define spatial averages

$$\bar{n}(t, a) := \frac{1}{h} \int_0^h n(t, a, x)\, dx \quad \text{and} \quad \bar{c}(t) := \frac{1}{h} \int_0^h c(t, x)\, dx \,.$$

Homogeneization result

Compartment size determination criterion: the population should converge to a spatially-uniform solution (fast enough) at the level of the mean field model.

Proposition (T. Alarcón, J.C., H.-W. Kang)

Let (n, c) be a solution pair of the mean field model in $[0, t) \times [0, h] \times [0, \infty)$ with zero Neumann spatial boundary conditions. Assume that $1/\tau_p > \nu$. Then, any choice of h satisfying

$$h < \sqrt{\frac{D_n}{1/\tau_p - \nu}}$$

ensures that

$$\int_0^\infty \int_0^h |n(t) - \bar{n}(t)| \, dxda \to 0 \quad \text{and} \quad \int_0^h |c(t) - \bar{c}(t)| \, dx \to 0$$

exponentially fast.

Homogeneization result, sketch of proof

Relative entropy (population)

$$H(f|g) := \int_0^\infty \int_0^h f(a,x) \log\left(\frac{f(a,x)}{g(a,x)}\right) \, dxda.$$

Evolution equation for the relative entropy:

$$\frac{d}{dt} H(n(t)|\bar{n}(t)) \leq -D_n \int_0^\infty \int_0^h \frac{(n_x)^2}{n} \, dxda + \int_0^\infty \int_0^h (b(a) - \nu) n \log\left(\frac{n}{\bar{n}}\right) \, dxda \, .$$

Homogeneization result, sketch of proof

Log-Sobolev inequality:

$$\int_0^h \phi^2 \log\left(\frac{h\,\phi^2}{\|\phi\|_2^2}\right) dx \le 2h^2 \|\phi_x\|_2^2, \quad \phi \in W^{1,2}(0,h)$$

(Stam, Gross, Holley, Stroock, ...)

Lower bound on Fisher's information:

$$\frac{1}{2h^2}\int_0^h n \log\left(\frac{n}{\bar{n}}\right) \le \int_0^h [(\sqrt{n})_x]^2\, dx\,.$$

Final estimate (through Cziszar–Kullback):

$$\int_0^\infty \int_0^h |n-\bar{n}|\, dxda \le \sqrt{2\|n(0)\|_{L^1_{a,x}} H(n(0)|\bar{n}(0))}$$

$$\times \exp\left\{-t\left(\frac{D_n}{h^2}+\nu-\frac{1}{\tau_p}\right)\right\}\,.$$

Homogeneization result, sketch of proof

Define relative entropy (oxygen concentration)

$$H(f|g) := \int_0^h f(x) \log\left(\frac{f(x)}{g(x)}\right) dx.$$

Using Cziszar–Kullback's inequality we get

$$\int_0^h |c - \bar{c}|\, dx \leq \sqrt{2h\bar{c}}\sqrt{H(c|\bar{c})}.$$

We close the loop by means of

$$H(c|\bar{c}) \leq H(c(t=0)|\bar{c}(t=0))\, e^{-t\left(k_2 + \frac{2D_c}{h^2}\right)}.$$

To sum up

$$\text{compartment size} < \sqrt{\frac{\text{diffusion coefficient}}{\text{birth rate - death rate}}}$$

Work in progress:

- Computational testing and comparison with fluctuation measures
- Sensible formulations in spatial dimension higher than one
- Extensions of the stochastic tissue model:
  - Competing populations
  - Therapies

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