MULTIPHASE AND MORPHO-PORO-ELASTIC MULTISCALE MODELS OF BIOLOGICAL TISSUE GROWTH

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Keywords: Multiscale asymptotics, Tissue growth, Porous flow.

The derivation of so-called 'effective descriptions' that explicitly incorporate microscale physics into a macroscopic model has garnered much attention, with popular applications in poroelasticity, and models of the subsurface in particular. More recently, such approaches have been applied to describe the physics of biological tissue. In such applications, a key feature is that the material is active, undergoing both elastic deformation and growth in response to local biophysical/chemical cues.

Here, two new macroscale descriptions of drug/nutrient-limited tissue growth are introduced, obtained by means of two-scale asymptotics. First, a multiphase viscous fluid model [1] is employed to describe the dynamics of a growing tissue within a porous scaffold (of the kind employed in tissue engineering applications) at the microscale. Secondly, the coupling between growth and elastic deformation is considered, employing a morpho-elastic description of a growing poroelastic medium. Importantly, in this work, the restrictive assumptions typically made on the underlying model to permit a more straightforward multiscale analysis are relaxed, by considering finite growth and deformation at the pore scale.

In each case, a multiple scales analysis provides an effective macroscale description, which incorporates dependence on the microscale structure and dynamics provided by prototypical 'unit cell-problems'. Importantly, due to the complexity that we accommodate, and in contrast to many other similar studies, these microscale unit cell problems are themselves parameterised by the macroscale dynamics. In the first case, the resulting model comprises a Darcy flow, and differential equations for the volume fraction of cells within the scaffold and the concentration of nutrient, required for growth. Stokes-type cell problems retain multiscale dependence, incorporating active cell motion [2]. Example numerical simulations indicate the influence of microstructure and cell dynamics on predicted macroscale tissue evolution. In the morpho-elastic model, the effective macroscale dynamics are described by

a Biot-type system, augmented with additional terms pertaining to growth, coupled to an advection–reaction–diffusion equation [3].

Improved models accommodating the interaction between subcellular, cellular and tissue-level behaviour are crucial to understanding tissue growth and mechanics; advances in this area have clear application to problems in tissue engineering and regenerative medicine. Here we provide two new multiscale models that accommodate detailed aspects of active cell behaviour, and finite growth and deformation, respectively.

References

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Cell and Intra-Cell Dynamics II

ACCURATE PREDICTION OF INTRACELLULAR CONCENTRATIONS IN *E. COLI* FROM A SIMPLE OPTIMALITY PRINCIPLE

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Keywords: Cell Biology, Metabolism, Protein Translation, Optimality principles.

A fundamental problem in biology is how cells organize their resource investment. Cellular metabolism and protein translation, for example, typically each involve hundreds of molecule types, but it is unclear according to which principles their concentrations are set. We propose that natural selection causes cells to minimize the total mass density required to carry out any given cellular process. The rationale for our hypothesis is the observation that the cytosolic mass density of cells is approximately constant across experimental conditions, possibly because this density represents the limit of the cytosolic solvent capacity. Any solute present in the cell utilizes a proportion of the available 'concentration space'. This space hence represents a limiting resource, which is optimally exploited if the total mass concentration of all molecules involved in each process is minimal.

In growing bacterial cells, a large fraction of cellular dry mass is occupied by the translation machinery. To test if natural selection minimized the summed mass concentration of translation components needed to achieve a given translation rate, we constructed a mathematical model of *E. coli* translation, fully parameterized with literature values and encompassing about 100 biochemical reactions. We minimize the combined mass concentration of ribosomes, mRNA, elongation factors, and charged tRNAs necessary for the protein production rate observed at a given growth rate. Without any free fitting parameters, the predictions agree accurately with measured concentrations and ribosomal elongation rates across multiple growth conditions.

We further derive a general equation that relates the concentration of a metabolite to the concentration of the most abundant and costly enzyme consuming it. For effectively irreversible reactions, optimal cellular investment is divided equally between unbound enzyme and substrate mass concentrations, a relationship independent of reaction rates and turnover numbers. Without fitting any free parameters, the resulting model predicts absolute *in vivo* substrate concentration from enzyme concentration and substrate affinity with high accuracy.

Thus, the minimization of the summed mass concentrations of solutes provides a fundamental rationale for cellular investment into different types of molecules.

PROLIFERATION RATE INFERENCE WITH CONTINUOUS LABELLING ASSAYS

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Keywords: Parameter Inference, Cell Biology.

Precise estimates of proliferation rates are crucial for quantitative models of the development and maintenance of tissues. Continuous labelling assays are a popular approach to infer proliferation rates in vivo. In these assays, proliferating cells take up a label, e.g. BrdU, when synthesizing DNA for cell division. Intuitively, more cells take up the label per time if they proliferate faster. So far, the experimental and theoretical study of continuous labelling assays focused on the dynamics of the mean labelling-fraction but not on the labelling-fraction distribution dynamics. To study this distribution dynamics, we developed a stochastic model of continuous labelling assays. With the model, we study the effects of cell and sample level noise in the distribution of cell cycle lengths. Using simulated data as ground truth, we show that current inference methods give biased proliferation rate estimates. Therefore, we derive analytical results for the Likelihood for our model that can be used to achieve unbiased estimates of the proliferation rates in vivo.

<u>Parallel Session</u>
Cell and Intra-Cell Dynamics II

ARCHITECTURES OF DIFFERENTIATION CASCADES WITH ASYMMETRIC AND SYMMETRIC STEM CELL DIVISION

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Keywords: Systems Biology, Stochastic Process, Master Equations, Evolutionary Dynamics.

The role of symmetric division in stem cell (SC) biology is ambiguous. It is necessary after injuries, but if symmetric divisions occur too often, the appearance of tumours is more likely. SC division is enough to keep alive the entire population in several tissues. However, that is not the liver after an injury hepatocytes have divide. To explore the role of symmetric and asymmetric division in different cell populations, we propose a mathematical model of competition of populations, in which SC expansion is controlled by fully differentiated cells. We explore the different configurations depending on different external factors . We show that there is an optimal fraction of symmetric stem cell division and an optimal number of SC, that maximises the long-term survival probability of the organism.

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<u>Parallel Session</u>
Cell and Intra-Cell Dynamics II

EXACT LOWER AND UPPER BOUNDS ON MOMENTS OF BIOCHEMICAL SYSTEMS

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Keywords: Systems biology, Stochastic chemical kinetics, Chemical master equation, Moment closure, Stochastic expression.

Biochemical systems often comprise of constituents that are present in small numbers, and consequently are more accurately characterized as stochastic systems. In the stochastic description, the time evolution of statistical moments for species population counts is described by a linear dynamical system. However, except for some ideal cases (such as zero- and first-order reaction kinetics), the moment dynamics is underdetermined as lower-order moments depend upon higher-order moments. One way to overcome this problem is to employ so-called moment closure methods that give point approximations to moments, but these are limited in that accuracy of the estimations is unknown. We propose a method to find exact lower and upper bounds on stationary moments for a given arbitrary system of biochemical reactions. Here we utilize the fact that statistical moments of any positive-valued random variable must satisfy some constraints that are compactly represented through the positive semidefiniteness of moment matrices. Our analysis shows that solving moment equations at steady state in conjunction with constraints on moment matrices provides exact lower and upper bounds on the moments. Furthermore, the accuracy of the bounds improves as moment equations are expanded to include higher-order moments. Our results provide avenues for development of methods that provide explicit bounds on moments for nonlinear stochastic systems that are otherwise analytically intractable.

Cell and Intra-Cell Dynamics II

CURVATURE-SENSITIVE KINESIN BINDING CAN INDUCE RINGS AND CHAOTIC DYNAMICS IN MICROTUBULES

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Keywords: Microtubules, Gliding assays, Inextensible filaments, Induced curvature.

Microtubules (MTs) are one of the main components of cells, and are essential for many biological functions. As the stiffest cytoskeletal polymer, they are generally seen to be very straight over cellular lengthscales. However, in areas of neurodegeneration highly curved MTs are seen with radius of curvature of a micron. Similarly curved MT rings are also sometimes seen in gliding assays, where MTs are moved over a surface by the motor protein kinesin, amongst other MTs translocating as rigid rods.

Recent evidence suggests that some microtubule-associated proteins such as kinesin are able to sense and alter MT curvature, and so we model MTs as inextensible rods with a preferred curvature, which is controlled by the differential binding of the kinesin. We find that there exist parameter regimes wherein metastable rings can form, and hence offer this differential binding as an explanation for these highly curved MTs seen *in vitro* and *in vivo*.

For certain parameter regimes, the model predicts that both straight and curved MTs can exist simultaneously as stable steady-states, as has been seen experimentally. Additionally, unsteady solutions are found, where a wave of differential binding propagates down the MT as it glides across the surface, which can lead to chaotic motion via a period doubling bifurcation.

We will also briefly discuss the use of the compound matrix method/Evans function for solving eigenvalue boundary value problems, which is available as a Mathematica package.