Mathematical analysis of PAR protein dynamics

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***Short Abstract* — Establishment and maintenance of cell polarity is a fundamental question in cell biology with the molecular protagonists, the PAR proteins, being conserved across the evolutionary spectrum. The following emergent behaviors are observed while constructing a mathematically rigorous yet biologically realistic model of PAR protein dynamics during different phases of cellular polarity generation: (a) Temporal bistability capturing PAR protein dynamics at the cortical-cytoplasmic interface during the maintenance phase; (b) Spatial bistability in PAR proteins dynamics resulting from domain specific protein segregation during establishment phase.**

***Keywords* — Par proteins, cell polarity, bistability.**

I. Introduction: The Biological Phenomenon

Polarity, a fundamental property of cells, is manifested in an intrinsic asymmetry with respect to protein localization or structural component distribution in specific compartments within the cell.[1] The fine-tuned segregation of protein scaffolds at different regions of a cell serves as demarcation of membrane domains, affects cell decision processes, serves as an intersection for signaling pathways, and contributes towards cell adhesion.[2,3] Polarization occurs concurrently with functional specialization and decisions made during the developmental chronology of a cell are contingent upon precise establishment and unfailing maintenance of the cell polarity. Development of polarity can be subdivided into the following stages: recognition of an extra-cellular cue followed by marking a cortical site in its response, transmission of the signal to rest of the cell leading to establishment of asymmetric domains of protein localization, and finally stable maintenance of these spatially segregated domains.[4,5] Genetic and biochemical studies have identified and characterized a set of evolutionarily conserved proteins (PAR proteins, aPKC, Cdc42) involved in establishment and maintenance of polarized state of cells in various contexts and model organisms (antero-posterior polarity in *C. elegans* embryo, apical-basal polarity in *Drosophila* follicular epithelium, embryonic ectoderm, neuroblasts and imaginal discs and mammalian epithelial cultured cells).

II. Strategy and Methodology

The overall goal of the project is to create a mathematically rigorous yet biologically realistic model of PAR protein function in generating asymmetric within cells. Sub-dividing the whole problem into mathematically tractable and computationally feasible parts, spatio-temporal dynamics of the PAR proteins is concentrated upon.

Towards this, a core module of the PAR proteins (Par-3, Par-6 and aPKC) is delineated from generic network diagram assimilated from published literature providing a graphical representation of reactions between the species of proteins involved.

These are chosen due to availability of biochemical and genetic experimental data and as a trade-off to preserve 'model-granularity' (evolutionarily conserved and functionally essential cassette of proteins yet model with reasonable predictive capacity). Thereafter, a set of coupled differential equations representing the rate of production and consumption of each biomolecular species is used to transform the network diagram into mathematical formalism. Mass action kinetics with continuum approximation (ignoring stochastic fluctuations) and compartmentalization in cellular milieu with unidimensional interface is assumed. Two models are constructed (a) *Spatially invariant model* considering only temporal dynamics of the protein species: Mathematical analysis performed on coupled ordinary differential equations (null-clines, phase portraits and bifurcation diagrams abstracting the system) along with numerical simulation using random parameter search to observe emergent behavior. (b) *Spatial model* incorporating spatial variation or diffusion effects: Mathematical analysis on coupled partial differential equations (Advection-Diffusion equation) and numerical simulation for implementing a traveling-wave solution.

III. Results and Conclusion

A. *Temporal bistability* in dynamics of PAR proteins in cytoplasmic and cortical cellular compartments is observed as emergent behavior in the spatially invariant model. This implies there are at least two stable steady states within biologically relevant ranges of protein concentrations coexisting with an unstable steady state. Depending on initial concentrations of proteins and appropriate tuning of biochemical interaction parameters, the system converges to either of the steady states with time, avoiding the unstable steady state, and stays in that state.

B. *Spatial bistability* in distribution of PAR proteins is observed in the model that takes into account mutually antagonistic interaction between PAR proteins localized in complementary domains. The dynamics of 'cortical flow' during establishment of asymmetric domains (in *C. elegans* embryo: clearing of Par-3, Par-6 and aPKC from the posterior domain after sperm entry, leading to their anterior enrichment, ensuing 'tug of war' from difference in contractility due to asymmetrically distributed myosin[6]) is captured in the form of a 'traveling wave' solution.

In summary, a paradigm, attempting to answer a fundamentally important cell biological question, is established with a potential to iterate between mechanistic characterization (by biological experimentation) and its mathematical simulation framework. It is hoped that with a complete analysis, emergent behavior, unknown so far, can be studied, thus providing experimentally testable hypotheses for validation.

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