Integration of Experimentation with Modeling

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Outline

- Rationale for integrated studies
- Stages of experimental integration into models
  - Framing the question
  - Choosing assumptions
  - Parameterization
  - Validation
  - Model refinement
- Examples of data integration into 2 models.

Rationale for Experimental Integration with Mathematical Models

- Usefulness of models depends upon ability to test or answer difficult biological questions
  - Avoid modeling for modeling sake
  - The dialogue between experimentalists and modelers is critical in setting up useful models
  - Specific experimental systems can help define general biological questions and provide a starting platform for modeling

Rationale for Experimental Integration with Mathematical Models

- Much of biology is context-dependent
  - Microenvironment-dependence of cellular responses: cancer, angiogenesis, etc.
  - Standardization of experimental conditions
  - using data purely from the literature can be misleading
  - Gathering data appropriate for models

Rationale for Experimental Integration with Mathematical Models

- The process of data integration is informative
  - Data frequently gathered in a different way: gives unexpected results
  - Simulation results inspire new experimental hypotheses
  - Model refinement, based on experimental results, leads to reconsideration of assumptions

Stages of Integration: framing the question

- What kind of question to ask with models?
  - Something that you can't fully answer with data alone
    - Complex systems: many variables
    - Experimentation technically difficult
  - Enough biology known to formulate reasonable assumptions
  - Broad enough to be of general interest…and/or…narrow enough to be used by others to answer specific questions

Stages of Integration: framing the question

- Examples of questions to ask?
  - What is the role of the microenvironment in regulating tumor invasion?
    - Specifics: ECM, growth factors, cellular heterogeneity, paracrine, autocrine interactions, intracellular responses
  - How are molecular changes converted into cellular and tissue phenotypes?
  - Can we predict drug response and resistance?
    - Different scales

Generation of Assumptions

- Often the most useful stage
- Sets structured theoretical framework for experimental work
- Use broad understanding from literature
- May require additional experimental work

Parameterization

- Uses:
  - Parameters are critical determinants of model results
  - Provide biological context: obtain parameters under certain microenvironmental conditions
  - Unanticipated or incompatible values may test assumptions
  - Model tuning: allows adaptation of model to specific experimental or biological systems

Model testing (validation)

- Testing whether model predictions are true
  - Broad vs. specific
  - Tells about context
    - Are assumptions correct?
    - Are there things missing from the model?
    - Are the conditions different?
  - Takes you forward into future work

Post-validation

- Model development
- Use of additional models