

The background features a dark blue gradient with a complex pattern of white and light blue circular elements. These include solid and dashed circles, some with arrows indicating direction, and a large circular scale with numerical markings from 140 to 260 in increments of 10. The overall aesthetic is technical and scientific.

# Genome-scale metabolic networks

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### 1. Draft reconstruction

- 1| Obtain genome annotation.
- 2| Identify candidate metabolic functions.
- 3| Obtain candidate metabolic reactions.
- 4| Assemble draft reconstruction.
- 5| Collect experimental data.

### 2. Refinement of reconstruction

- 6| Determine and verify substrate and cofactor usage.
- 7| Obtain neutral formula for each metabolite.
- 8| Determine the charged formula.
- 9| Calculate reaction stoichiometry.
- 10| Determine reaction directionality.
- 11| Add information for gene and reaction localization.
- 12| Add subsystems information.
- 13| Verify gene-protein-reaction association.
- 14| Add metabolite identifier.
- 15| Determine and add confidence score.
- 16| Add references and notes.
- 17| Flag information from other organisms.
- 18| Repeat Steps 6 to 17 for all genes.
- 19| Add spontaneous reactions to the reconstruction.
- 20| Add extracellular and periplasmic transport reactions.
- 21| Add exchange reactions.
- 22| Add intracellular transport reactions.
- 23| Draw metabolic map (optional).
- 24–32| Determine biomass composition.
- 33| Add biomass reaction.
- 34| Add ATP-maintenance reaction (ATPM).
- 35| Add demand reactions.
- 36| Add sink reactions.
- 37| Determine growth medium requirements.

### 4. Network evaluation

- 43–44| Test if network is mass-and charge balanced.
- 45| Identify metabolic dead-ends.
- 46–48| Perform gap analysis.
- 49| Add missing exchange reactions to model.
- 50| Set exchange constraints for a simulation condition.
- 51–58| Test for stoichiometrically balanced cycles.
- 59| Re-compute gap list.
- 60–65| Test if biomass precursors can be produced in standard medium.
- 66| Test if biomass precursors can be produced in other growth media.
- 67–75| Test if the model can produce known secretion products.
- 76–78| Check for blocked reactions.
- 79–80| Compute single gene deletion phenotypes.
- 81–82| Test for known incapacities of the organism.
- 83| Compare predicted physiological properties with known properties.
- 84–87| Test if the model can grow fast enough.
- 88–94| Test if the model grows too fast.

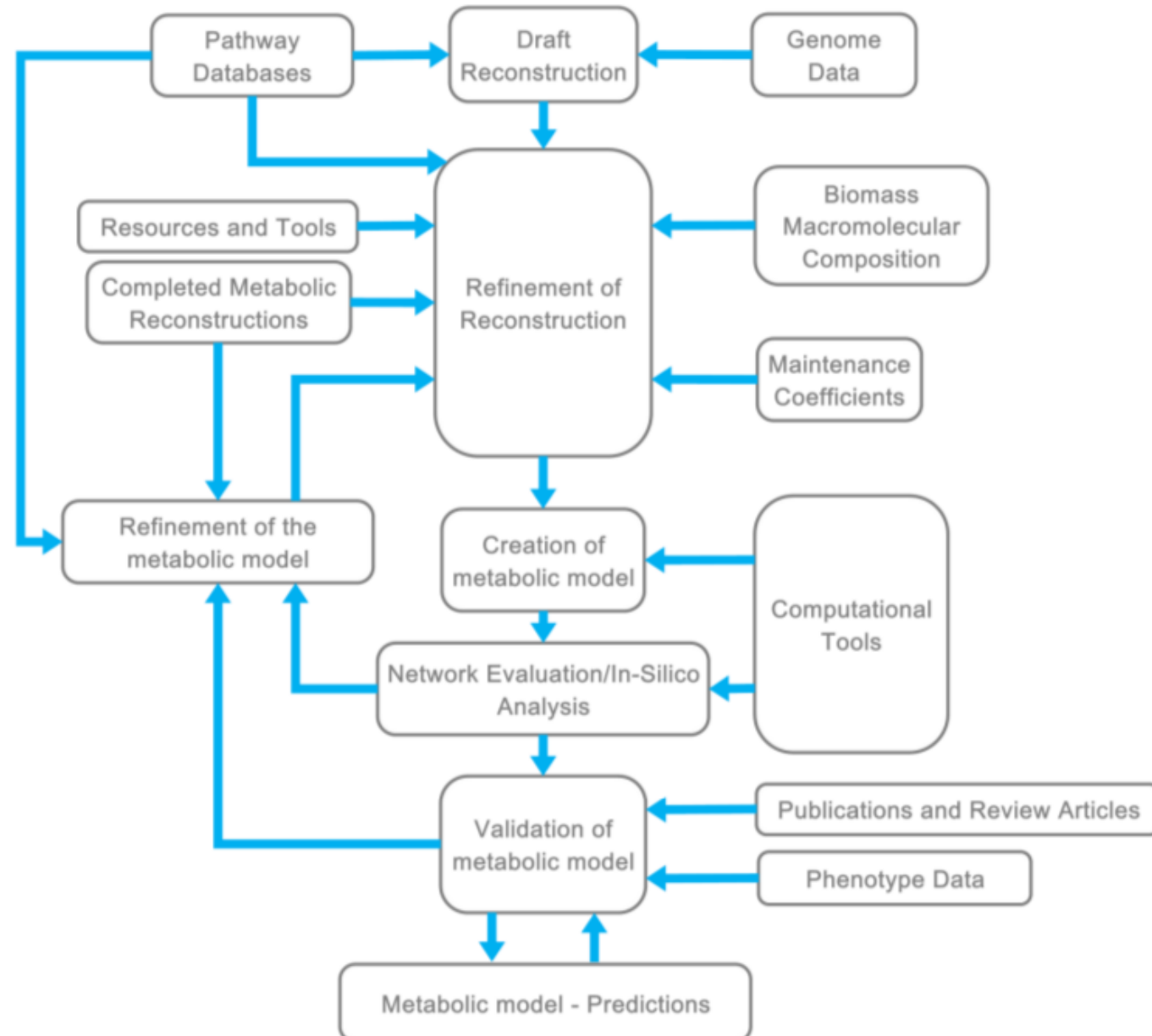
### 3. Conversion of reconstruction into computable format

- 38| Initialize the COBRA toolbox.
- 39| Load reconstruction into Matlab.
- 40| Verify S matrix.
- 41| Set objective function.
- 42| Set simulation constraints.

### Data assembly and dissemination

- 95| Print Matlab model content.
- 96| Add gap information to the reconstruction output.

Thiele, Ines, and Bernhard Ø. Palsson. "A protocol for generating a high-quality genome-scale metabolic reconstruction." Nature protocols 5.1 (2010): 93-121.

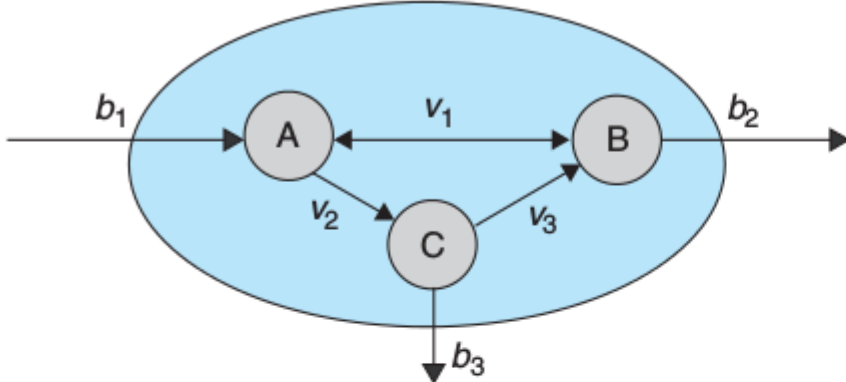


**Fig. 1 Genome-scale metabolic network reconstruct process**

杨毅. 大豆慢生根瘤菌基因组规模代谢网络构建与分析[D]. 华中农业大学, 2014.

# MODEL DEVELOPMENT

## The Stoichiometric Matrix

(a) 

(b) Material Balances

$$\frac{dA}{dt} = -v_1 - v_2 + b_1$$

$$\frac{dB}{dt} = v_1 + v_3 - b_2$$

$$\frac{dC}{dt} = v_2 - v_3 - b_3$$

(c) 
$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} -1 & -1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & -1 & 0 & 0 & -1 \end{bmatrix} \cdot \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ b_1 \\ b_2 \\ b_3 \end{bmatrix}$$

(d) Subject to:

Steady-state	Reaction stoichiometry pH	Kinetic Thermodynamic
$0 = S \cdot v$		$-\infty \leq v_1 \leq \infty$ $\infty \leq v_2 \leq \infty$ $\infty \leq v_3 \leq \infty$
		$0 \leq b_1 \leq 10$ $0 \leq b_2 \leq 10$ $0 \leq b_3 \leq \infty$

Objective: maximize  $b_2$

Constraints on Reaction Rates

Links to Genomic Information—GPR relationship



# STOICHIOMETRIC NETWORK ANALYSIS

## Structural Analysis: Characterizing the Nullspace

$$v = a_1 \cdot K_1 + a_2 \cdot K_2 + \dots + a_n \cdot K_n = K \cdot a$$

$$\begin{bmatrix} v_1 \\ v_2 \\ \dots \\ v_n \end{bmatrix} = \begin{bmatrix} k_{11} & k_{21} & \dots & k_{n1} \\ k_{12} & k_{22} & \dots & k_{n2} \\ \dots & \dots & \dots & \dots \\ k_{1n} & k_{2n} & \dots & k_{nn} \end{bmatrix} \cdot \begin{bmatrix} a_1 \\ a_2 \\ \dots \\ a_n \end{bmatrix}$$

## RESULTS OF NULLSPACE ANALYSIS

1. If the kernel matrix contains a zero-row, the corresponding reaction cannot carry a (non-zero) flux. We can remove this reaction for all analysis employing the steady-state assumption.
2. If two matrix rows differ only by a constant factor, the two reactions are coupled, that is, the flux through one reaction is always a multiple of the flux through the other reaction; consequently either both reactions are active or both are passive. Such reactions are presumably co-regulated
3. Given reversibility constraints, inconsistent reaction coupling can be detected. For example, two coupled forward-only reactions with a negative coupling factor cannot carry a non-zero flux without violating an irreversibility constraint, since one reaction would have to operate in backward mode.

# STOICHIOMETRIC NETWORK ANALYSIS

## MODEL CONSISTENCY

1. Minimize and maximize the flux value for each reaction.

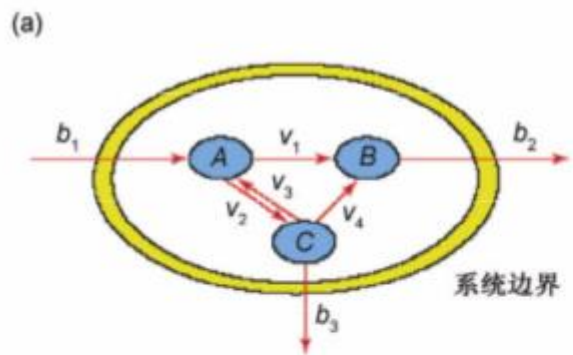
(a) If min and max value are zero, the reaction is a zero flux reaction, that is, it cannot have a flux value other than zero. It can be removed if no model corrections are made, without affecting the outcome of subsequent simulations.

(b) If min or max value is zero and the reaction is reversible, we have an unsatisfied reversibility. Either the reversibility constraint is too lax or another component is missing, disabling the operation in one direction. Tightening this constraint might lead to better simulation performance.

(c) If the minimal and maximal values are non-zero and have equal sign, the reaction is essential. Deletion of the reaction, for example, by gene knockout, is predicted to be lethal.

2. For reactions not of type (1c), set the bounds to zero. If biomass cannot be produced, the reaction is essential. Again, reaction removal is associated with lethality.

# FBA—flux balance analysis



(b)

$$\frac{dA}{dt} = -v_1 - v_2 + v_3 + b_1$$

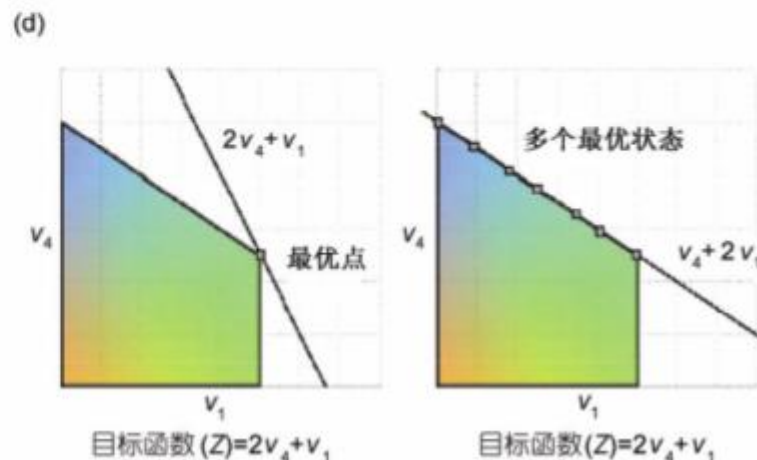
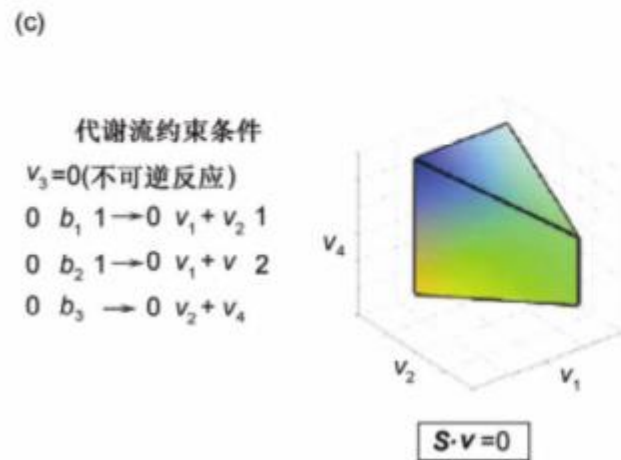
$$\frac{dB}{dt} = v_1 + v_4 - b_2$$

$$\frac{dC}{dt} = -v_2 - v_3 - v_4 - b_3$$

$$\begin{bmatrix} \frac{dA}{dt} \\ \frac{dB}{dt} \\ \frac{dC}{dt} \end{bmatrix} = \begin{bmatrix} -1 & -1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & -1 & -1 & 0 & 0 & -1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ b_1 \\ b_2 \\ b_3 \end{bmatrix}$$

← S →

↑ V ↓

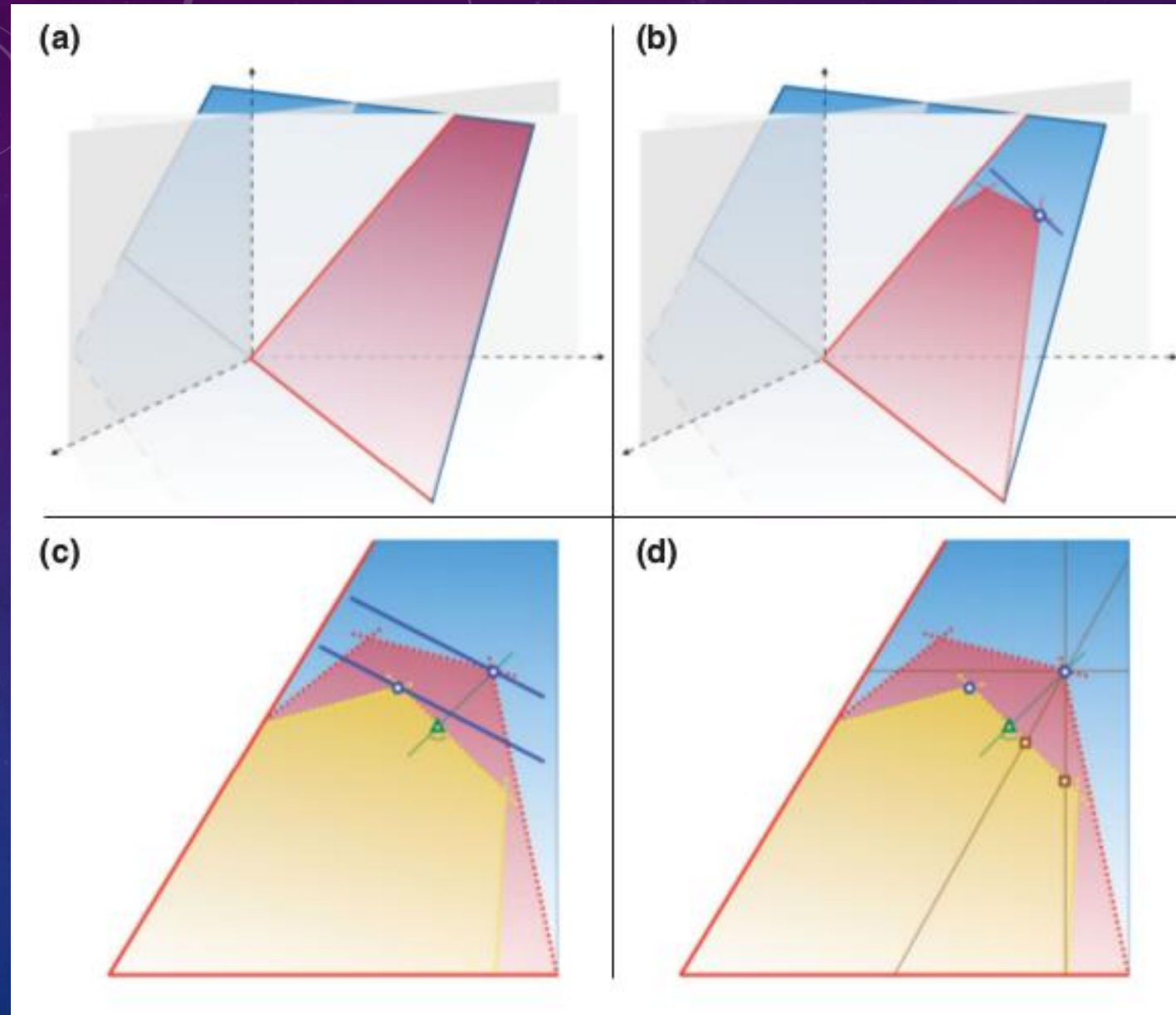




Deletion Strain Phenotypes

Minimization of metabolic adjustment (MoMA)

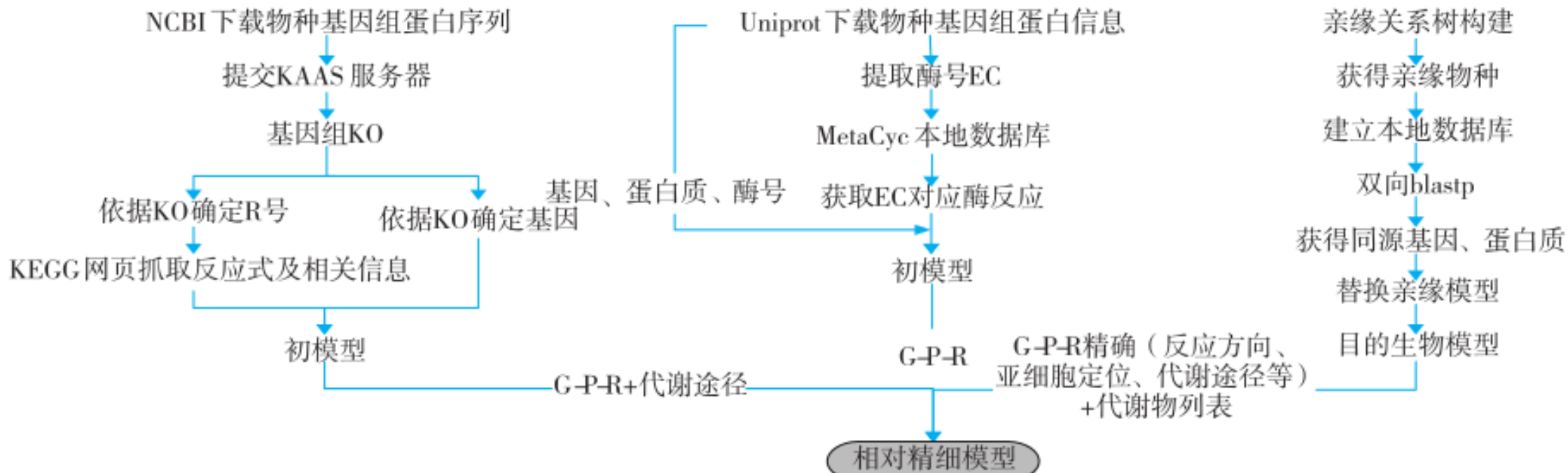
Regulatory on/off minimization (ROOM)





	CellNetAnalyzer FluxAnalyzer	BioSPICE MOMA	COBRA Tool- box	FluxExplorer	MetaFluxNet	Pathway Analyser	Fbatool
图形化界面	有	有	无	有	有	无	无
网络构建方法	Four Network Element files	SBML files	SBML files	Mannually	SBML files	SBML files	SBML files
适用操作系统	Windows (Matlab)	Windows Linux	Windows (Matlab)	Windows	Windows	Linux UNIX	Corona
网络分析算法	MFA SNA	FBA MOMA	FBA MOMA DFBA FVA	FBA MOMA EPA SVD	MFA	FBA MOMA	FBA
适用网络规模	中	大	大	小	大	大	大
操作难易程度	易	难	中	易	易	中	中
软件可用性	优	良	优	中	良	良	中

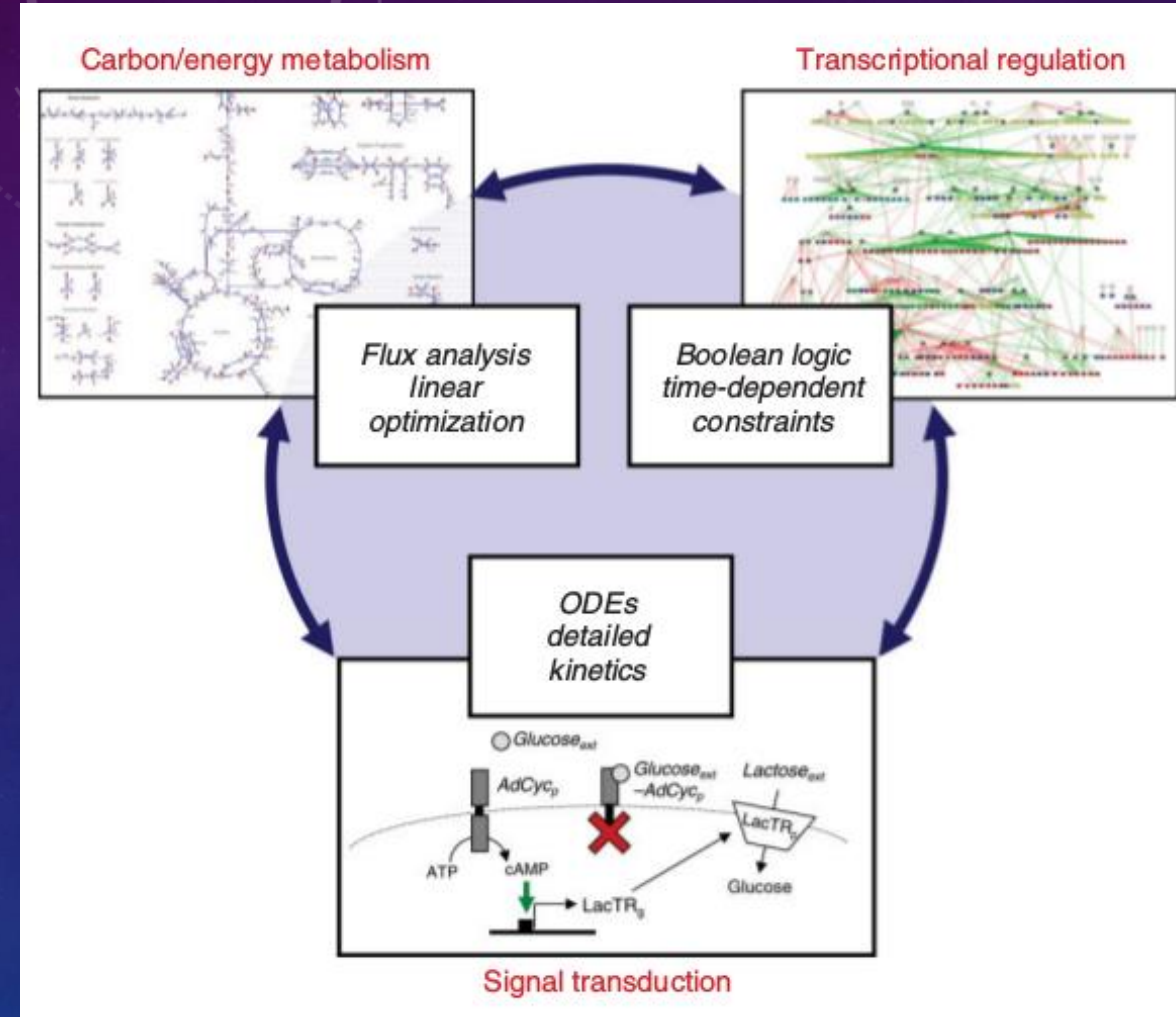
1、Automated Network Reconstruction



# CURRENT CHALLENGES

2、 Cellular Optimality and Design

3、 Toward Large-Scale Network Integration and Dynamics





The background features a dark blue gradient with a subtle pattern of white stars. Overlaid on this are several technical diagrams in a lighter blue color. These include circular gauges with numerical scales (e.g., 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260), dashed lines, and various circular and semi-circular shapes, some with arrows indicating direction or flow. The overall aesthetic is clean and professional, suggesting a technical or scientific context.

Thanks for your listening!