CLAIMS

What is claimed is:

1. A method implemented by a data processing system for outputting one or more predictive models for developing or operating a process for a cell or gene therapy (CGT), comprising:

receiving a plurality of data items corresponding to features of the process for the cell or gene therapy;

storing the plurality of data items on a hardware storage device;

accessing the plurality of data items using the data processing system;

determining, by the data processing system, one or more attributes of the plurality of data items, wherein the one or more attributes characterize mathematical relationships of the plurality of data items in a prediction for the process for the cell or gene therapy;

selecting one or more machine learning models based on the one or more attributes of the plurality of data items corresponding to the features of the process for the cell or gene therapy;

accessing one or more mechanistic models;

integrating, by the data processing system, the one or more machine learning models with the one or more mechanistic models to obtain one or more integrated models;

selecting one or more predictive models from the one or more machine learning models, the one or more mechanistic models, and the one or more integrated models, wherein the one or more predictive models predict one or more internal cell states and/or performance of the process for the cell or gene therapy;

applying the one or more predictive models to the plurality of data items;

adjusting one or more values of one or more parameters of the one or more predictive models to reduce uncertainty in model prediction; and

outputting, by the data processing system, the one or more predictive models with the one or more adjusted values of the one or more parameters,

whereby the one or more predictive models with the one or more adjusted values of the one or more parameters are applied to the process for the cell or gene therapy to reduce uncertainty in predictions of the one or more internal cell states and/or performance of the process for the cell or gene therapy.

2. The method of claim 1, wherein the one or more attributes comprise at least one of: nonlinearity; collinearity; nonnormality; or dynamics.

3. The method of claim 1, wherein the one or more mechanistic models are accessed based on at least one of a physical property, a chemical property, or a biological property of the process.

4. The method of claim 1, wherein integrating the one or more machine learning models with the one or more mechanistic models comprises:

arranging the one or more machine learning models and the one or more mechanistic models in a sequence comprising a first one or more models and a second one or more models;

transmitting an output of the first one or more models to the second one or more models;

transmitting data to the second one or more models; and

obtaining an output of the second one or more models.

5. The method of claim 1, wherein integrating the one or more machine learning models with the one or more mechanistic models comprises:

determining a first one or more models and a second one or more models from the one or more machine learning models and the one or more mechanistic models;

transmitting input data to the first one or more models;

constraining a prediction of the first one or more models using the second one or more models; and

obtaining an output of the first one or more models.

6. The method of claim 1,

wherein the plurality of data items is obtained from a cell population of a first type,

wherein the method further comprises:

causing production of a cell population of a second type using one or more output models, and

wherein the second type is different from the first type.

7. The method of claim 6, wherein each of the cell population of the first type and the cell population of the second type comprises at least one of: heterogeneous cell populations; or clonal cell populations.

8. The method of claim 7, wherein the heterogeneous cell populations have at least one of: intracellular heterogeneity; or cell surface heterogeneity.

9. The method of claim 1, further comprising:

causing production of a stable cell line using one or more output models.

10. The method of claim 9, wherein the stable cell line comprises at least one of:

HEK293 cells; HEK293T cells; Sf9 cells; HeLa cells, A469 cells; CAP cells; AGELHN cells; Per.C6 cells; NS01 cells; COS-7 cells; BHK cells; CHO cells; VERO cells; MDCK cells; BRL3A cells; HepG2 cells; primary human cells; peripheral blood mononuclear cells (PBMC); immune cells, T-cells; human stem cells; induced pluripotent stem cells; or somatic cells.

11. The method of claim 1, wherein a scale of the CGT is within a range of 1 mL per production run to 25,000 L per production run.

12. The method of claim 1, wherein the CGT uses one or more output models in cells grown for at least one mode of:

batch; fed-batch; perfusion; continuous; semi-continuous; or hybrid of fed-batch and perfusion.

13. The method of claim 1, wherein the CGT uses one or more output models to cause an automated or semi-automated production.

14. The method of claim 13, wherein the production is in a closed or semi-closed system.

15. The method of claim 1, wherein the CGT comprises a gene therapy.

16. The method of claim 15, wherein the gene therapy comprises using one or more payloads for at least one of:

gene replacement; gene activation; gene inactivation; introducing a new or modified gene; or gene editing.

17. The method of claim 15, further comprising:

causing generation of one or more viral vectors for the gene therapy using one or more output models.

18. The method of claim 17, where the viral vector comprises at least one of:

Adeno-associated virus; Lentivirus; Adenovirus; Baculovirus; Herpes Simplex Virus; Retrovirus; Oncolytic virus; Parvovirus; Annellovirus; or a Bacteriophage.

19. The method of claim 15, further comprising:

causing performance of transient transfection, stable transfection, or transduction for the gene therapy using one or more output models.

20. The method of claim 18, further comprising: causing performance of transient transfection, stable transfection, or transduction of suspension or adherent cells.

21. The method of claim 20, wherein the suspension or adherent cells comprise at least one of:

HEK293 cells; HEK293T cells; Sf9 cells; HeLa cells, A469 cells; CAP cells, AGELHN cells; Per.C6 cells; NS01 cells; COS-7 cells; BHK cells; CHO cells; VERO cells; MDCK cells; BRL3A cells; HepG2 cells; primary human cells; peripheral blood mononuclear cells (PBMC); immune cells, T-cells; human stem cells; induced pluripotent stem cells; or somatic cells.

22. The method of claim 15, further comprising:

causing performance of transfection or transduction of one or more stable producer host cell lines or one or more packaging host cell lines for the gene therapy using one or more output models.

23. The method of claim 15, further comprising:

causing production of a viral vector in a system without transfection.

24. The method of claim 15,

wherein the plurality of data items is obtained from transient transfection, and

wherein the method further comprises:

causing development and/or production of a stable producer cell line or a packaging cell line for the gene therapy using one or more output models.

25. The method of claim 15, wherein the gene therapy includes one or more targeting moieties.

26. The method of claim 25, wherein the one or more targeting moieties comprise at least one of:

a nucleic acid sequence; a protein; a protein fragment; a peptide; a monosaccharide; a polysaccharide; a small molecule; an aptamer; a dendrimer, or a centyrin.

27. The method of claim 1, further comprising:

causing production of a nucleic acid-based therapy or vaccine for the GCT using one or more output models.

28. The method of claim 27, further comprising:

causing production of a nucleic acid for the nucleic acid-based therapy or vaccine using the one or more output models.

29. The method of claim 27, wherein the nucleic acid therapy or vaccine comprises at least one of:

DNA, plasmid DNA (pDNA), RNA, messenger RNA (mRNA), small activating RNA (saRNA), small interfering RNA (also known as short interfering RNA, silencing RNA, or siRNA), microRNA (miRNA), circular RNA, antisense oligonucleotide (ASO), doggybone DNA (dbDNA), closed-ended DNA (ceDNA), synthetic DNA, or a non-natural nucleic acid.

30. The method of claim 27, further comprising:

causing a chemical or enzymatic modification of the nucleic acid.

31. The method of claim 27, wherein the nucleic acid is combined with a non-viral carrier.

32. The method of claim 27, wherein the production comprises at least one of:

a non-viral carrier; or a physical delivery method.

33. The method of claim 27, further comprising:

causing production of one or more sequences with a plurality of nucleic acid molecules for the nucleic acid-based therapy or vaccine.

34. The method of claim 27, wherein the nucleic acid-based therapy or vaccine comprises one or more nucleic acid molecules and one or more targeting moieties.

35. The method of claim 34, wherein the one or more targeting moieties comprise at least one of:

a nucleic acid sequence; a protein; a protein fragment; a peptide; a monosaccharide; a polysaccharide; a small molecule; an aptamer; a dendrimer, or a centyrin.

36. The method of claim 27, wherein the nucleic acid-based therapy or vaccine comprises one or more nucleic acid molecules and one or more non-nucleic acid molecules.

37. The method of claim 36, wherein the one or more non-nucleic acid molecules comprise a protein, a protein fragment, or a peptide.

38. The method of claim 27, wherein the nucleic acid-based therapy or vaccine is applied to at least one of: immune cells; tumor cells; cardiac cells; ocular cells; retinal cells; lung cells; muscle cells; skin cells; liver cells; pancreatic cells; intestinal cells; brain cells; or neurological cells.

39. The method of claim 32, wherein the non-viral carrier comprises at least one of: a lipid nanoparticle; a solid lipid nanoparticle; a nanostructured lipid carrier, a liposome; a lipoplex; a polymeric nanoparticle; a lipid-polymer hybrid nanoparticle; an inorganic nanoparticle; an exosome; a virus-like particle; an extracellular vesicle; a cell-penetrating peptide; a cationic polymer; an aptamer; a dendrimer; or a centyrin.

40. The method of claim 32, wherein the physical delivery method comprises at least one of: electroporation; cell squeezing; needles; patches; iontophoresis; biolistic delivery; sonoporation; ultrasound-mediated microbubbles; hydroporation; photoporation; or magnetofection.

41. The method of claim 1, wherein the CGT comprises a cell therapy.

42. The method of claim 41, further comprising:

causing generation of one or more cells for the cell therapy based on one or more output models,

wherein the one or more cells comprise at least one of: an autologous cell; or an allogeneic cell.

43. The method of claim 41, further comprising a cell therapy created by transduction with a viral vector or transfection with a nucleic acid.

44. The method of claim 41, wherein the cell therapy is applied to at least one of: immune cells; tumor cells; cardiac cells; ocular cells; retinal cells; lung cells; pancreatic cells; intestinal cells; kidney cells; muscle cells; skin cells; liver cells; brain cells; or neurological cells.

45. The method of claim 44, wherein the cell therapy is applied to the tumor cells associated with hematological malignancies or solid tumors.

46. The method of claim 41, wherein the cell therapy comprises production of at least one of: a modified chimeric antigen receptor T-cell (CAR T-cell); a gamma delta T-cell; a

natural killer (NK) cell; an engineered T-cell receptor (TCR); a tumor-infiltrating lymphocyte (TIL); a macrophage; a dendritic cell; a hematopoetic stem cell (HSC); or a mesenchymal stem/stromal cell (MSC).

47. The method of claim 41,

wherein the one or more cells comprise an autologous cell that is prepared from a source comprising at least one of: a stem cell, a pluripotent stem cell, a non-stem cell, or a cell line,

wherein the autologous cell is derived from a source comprising at least one of: peripheral blood; bone marrow; umbilical cord blood; placenta; skin; eye; muscle; or tumor.

48. The method of claim 41, wherein the one or more cells comprise an allogeneic cell that is prepared from a source comprising at least one of: peripheral blood mononuclear cells (PBMCs); umbilical cord blood; stem cells; or skin cells.

49. The method of claim 41, further comprising: causing the one or more cells to be edited.

50. The method of claim 41, further comprising: causing one or more genes in the one or more cells to be edited.

51. The method of claim 41, wherein the cell therapy comprises one or more targeting moieties.

52. The method of claim 51, wherein the one or more targeting moieties comprise at least one of:

a nucleic acid sequence; a protein; a protein fragment; a peptide; a monosaccharide; a polysaccharide; a small molecule; an aptamer; a dendrimer, or a centyrin.

53. The method of claim 41, wherein the cell therapy comprises ex vivo cell therapy.

54. The method of claim 41, wherein the cell therapy comprises at least one of: regenerative medicine; stem cell therapy; or tissue engineering.

55. The method of claim 41, wherein the cell therapy comprises in vivo cell therapy.

56. The method of claim 55, wherein the in vivo cell therapy comprises at least one of: endogenous production of a modified chimeric antigen receptor T cell (CAR T-cell); a natural killer (NK) cell; an engineered T-cell receptor (TCR); a tumor-infiltrating lymphocyte (TIL); or a macrophage.

57. The method of claim 1, wherein the CGT comprises a non-genetically modified cell therapy.

58. The method of claim 57, wherein the non-genetically modified cell therapy comprises at least one of: regenerative medicine; or tissue engineering.

59. A non-transitory computer-readable medium containing program instructions that, when executed, cause a data processing system to perform operations for developing or operating a process for a cell or gene therapy (CGT), the operations comprising:

receiving a plurality of data items corresponding to features of the process for the cell or gene therapy;

storing the plurality of data items on a hardware storage device;

accessing the plurality of data items;

determining one or more attributes of the plurality of data items, wherein the one or more attributes characterize mathematical relationships of the plurality of data items in a prediction for the process for the cell or gene therapy;

selecting one or more machine learning models based on the one or more attributes of the plurality of data items corresponding to the features of the process for the cell or gene therapy;

accessing one or more mechanistic models;

integrating the one or more machine learning models with the one or more mechanistic models to obtain one or more integrated models;

selecting, from the one or more machine learning models, the one or more mechanistic models, and the one or more integrated models, one or more predictive models, wherein the one or more predictive models predict one or more internal cell states and/or performance of the process for the cell or gene therapy;

applying the one or more predictive models to the plurality of data items;

adjusting one or more values of one or more parameters of the one or more predictive models to reduce uncertainty in model prediction; and

outputting the one or more predictive models with the one or more adjusted values of the one or more parameters,

whereby the one or more predictive models with the one or more adjusted values of the one or more parameters are applied to the process for the cell or gene therapy to reduce uncertainty in predictions of the one or more internal cell states and/or performance of the process for the cell or gene therapy.