

CLAIMS

What is claimed is:

1. A system for determining an impact of a therapeutic agent on diseased cells, comprising:
one or more processors;
a memory; and
one or more programs, wherein the one or more programs are stored in the memory and configured to be executed by the one or more processors, the one or more programs including instructions for:
 - obtaining a first plurality of images captured at a first plurality of time points of one or more untreated diseased live biological cells expressing a disease phenotype;
 - obtaining a second plurality of images captured at a second plurality of time points of one or more treated diseased live biological cells expressing the disease phenotype that has been treated with the therapeutic agent;
 - inputting the first plurality of images into a trained machine-learning model to obtain a first plurality of embedding vectors representing positional and morphological changes over time in particular cellular substructures of the one or more untreated diseased live biological cells;
 - inputting the second plurality of images into the trained machine-learning model to obtain a second plurality of embedding vectors representing positional and morphological changes over time in particular cellular substructures of the one or more treated diseased live biological cells; and
 - determining, from at least a subset of the first plurality of embedding vectors and the second plurality of embedding vectors, the impact of the therapeutic agent on a reversion of the one or more treated diseased live biological cells from a diseased state.
2. The system according to claim 1, further comprising:
 - obtaining a third plurality of images captured at a third plurality of time points of one or more healthy live biological cells;
 - inputting the third plurality of images into the trained machine-learning model to obtain a

third plurality of embedding vectors representing positional and morphological changes over time in particular cellular substructures of the one or more healthy live biological cells; and

determining, from at least a subset of the first plurality of embedding vectors, the second plurality of embedding vectors, and the third plurality of embedding vectors, the impact of the therapeutic agent on the reversion of the one or more treated diseased live biological cells from the diseased state to a healthy state.

3. The system according to claim 2, wherein the one or more treated diseased live biological cells are a first set of treated diseased live biological cells and are treated with a first dosage of the therapeutic agent; and the one or more programs further include instructions for:

- obtaining a fourth plurality of images captured at a fourth plurality of time points of a second set of treated diseased live biological cells expressing the disease phenotype that has been treated with a second dosage of the therapeutic agent;

- inputting the fourth plurality of images into the trained machine-learning model to obtain a fourth plurality of embedding vectors representing positional and morphological changes over time in particular cellular substructures of the second set of treated diseased live biological cells; and

- comparing the impact of the first dosage and the second dosage based on at least a subset of the first plurality of embedding vectors, the second plurality of embedding vectors, and the fourth plurality of embedding vectors;

and optionally

- obtaining a fifth plurality of images captured at a fifth plurality of time points of a third set of treated diseased cells expressing the disease phenotype that has been treated with a second therapeutic agent;

- inputting the fifth plurality of images into the trained machine-learning model to obtain a fifth plurality of embedding vectors representing positional and morphological changes over time in particular cellular substructures of the third set of treated diseased live biological cells; and

comparing the impact of the first therapeutic agent and the second therapeutic agent based on at least a subset of the first plurality of embedding vectors, the second plurality of embedding vectors, and the fifth plurality of embedding vectors.

4. The system according to claim 1, wherein one of:

the first plurality of time points are the same as the second plurality of time points;
the first plurality of time points are different from the second plurality of time points;
the therapeutic agent is a chemical treatment, a genetic treatment, or any combination thereof;

the one or more programs further include instructions for determining one or more dose administration intervals for the therapeutic agent based on the second plurality of embedding vectors;

the one or more programs further include instructions for determining a medical recommendation for administering the therapeutic agent for a patient;

the first plurality of images and the second plurality of images comprise phase images;

the first plurality of images and the second plurality of images are generated from fluorescence images or autofluorescence images;

the trained machine-learning model is a self-supervised machine-learning model; or

the trained machine-learning model is trained using unlabeled data, optionally wherein the trained machine-learning model is pre-trained using unlabeled images that do not depict biological samples, and optionally wherein the trained machine-learning model is retrained using unlabeled images of biological samples.

5. The system according to claim 1, wherein or:

evaluating the impact of the therapeutic agent comprises:

inputting the first plurality of embedding vectors into a trained classifier to obtain a first plurality of disease scores, wherein the trained classifier is a model configured to receive an input embedding and output a corresponding disease score; and

inputting the second plurality of embedding vectors into the classifier to

obtain a second plurality of disease scores.

6. The system according to claim 5, further comprising:

- (i) generating a first time trend based on the first plurality of disease scores, generating a second time trend based on the second plurality of disease scores and comparing the first time trend and the second time trend;
- (ii) generating a first plurality of distributions based on the first plurality of disease scores, generating a second plurality of distributions based on the second plurality of disease scores and comparing the first plurality of distributions and the second plurality of distributions; or
- (iii) wherein the classifier is a logistic regression classifier.

7. The system according to claim 1, wherein

determining the impact of the therapeutic agent on the reversion of the one or more treated diseased live biological cells from the diseased state comprises:

identifying a first plurality of positions in a latent space corresponding to the first plurality of embedding vectors;

identifying a second plurality of positions in the latent space corresponding to the second plurality of embedding vectors; and

determining the impact of the therapeutic agent by comparing the first plurality of positions in the latent space and the second plurality of positions in the latent space.

8. The system according to claim 7, wherein

determining the impact of the therapeutic agent comprises determining a movement in the latent space based on the first plurality of positions in the latent space and the second plurality of positions in the latent space.

9. A system for modeling a progression of a disease of interest having a plurality of disease states, comprising:

one or more processors;

memory; and

one or more programs, wherein the one or more programs are stored in the memory and configured to be executed by the one or more processors to:

obtain a first set of images captured at a first plurality of time points of a first non-zero concentration of diseased live biological cells expressing a first disease state of the disease;

obtain a second set of images captured at a second plurality of time points of a second non-zero concentration of diseased live biological cells expressing a second disease state of the disease;

input the first set of images into a trained machine-learning model to obtain a first set of embeddings representing positional and morphological characteristics in particular cellular substructures of the first non-zero concentration of diseased live biological cells;

input the second set of images into the trained machine-learning model to obtain a second set of embeddings representing positional and morphological characteristics in particular cellular substructures of the second non-zero concentration of diseased live biological cells;

generate a disease model based on the first set of embeddings and the second set of embeddings; and

model a progression of the disease based on the disease model.

10. The system according to claim 9, wherein
 - generating a disease model comprises mapping the first set of embeddings and the second set of embeddings into a topological space;
 - optionally wherein the one or more programs further include instructions to identify a location of a first cluster of embeddings based on the first set of embeddings in the topological space, generate a representation of the first disease state based on the location of the first cluster, identify a location of a second cluster of embeddings based on the second set of embeddings in the topological space, and generate a representation of the second disease state based on the location of the second cluster;
 - and optionally wherein the first set of embeddings and the second set of embeddings are time-stamped in the topological space.
11. The system according to claim 9, wherein
 - the one or more programs, when executed by the one or more processors, cause the system to:

apply a therapeutic agent to the first non-zero concentration of diseased live biological cells;

obtain a plurality of images captured at a plurality of time points of the first non-zero concentration of diseased live biological cells;

input the plurality of images into the trained machine-learning model to obtain a plurality of embeddings representing positional and morphological changes over time in particular cellular substructures of the first non-zero concentration of diseased live biological cells; and

determine, from at least a subset of the plurality of embeddings, an impact of the therapeutic agent on a reversion of the first non-zero concentration of diseased live biological cells from a diseased state.

12. The system according to claim 11, wherein
one of:

the therapeutic agent is a chemical treatment, a genetic treatment, or any combination thereof;

the one or more programs further include instructions to determine a dosage for the therapeutic agent based on the plurality of embeddings;

the one or more programs further include instructions to determine one or more dose administration intervals for administering the therapeutic agent based on the plurality of embeddings;

the one or more programs further include instructions for providing a medical recommendation for administering the therapeutic agent to a patient having the disease; or

the one or more programs further include instructions to evaluate a treatment candidate, wherein evaluating the treatment candidate comprises inputting the plurality of embeddings to a classifier to obtain a plurality of disease scores and generating a time trend based on the plurality of disease scores, optionally where evaluating the treatment candidate comprises generating a plurality of distributions based on the plurality of disease scores or where the classifier is a logistic regression model.

13. The system according to claim 1, wherein
one of:

the first set of images and the second set of images comprise phase images;
the first set of images and the second set of images are generated based on fluorescence images or autofluorescence images;
the trained machine-learning model is a self-supervised machine-learning model, optionally wherein the trained machine-learning model comprises a neural network; or
the trained machine-learning model is pre-trained using unlabeled images that do not depict biological samples, optionally wherein the trained machine-learning model is configured to be retrained using unlabeled images of biological samples.

14. A method of modeling a progression of a disease of interest having a plurality of disease states, comprising:

obtaining a first set of images captured at a first plurality of time points of a first non-zero concentration of diseased live biological cells expressing a first disease state of the disease;

obtaining a second set of images captured at a second plurality of time points of a second non-zero concentration of diseased live biological cells expressing a second disease state of the disease;

inputting the first set of images into a trained machine-learning model to obtain a first set of embeddings representing positional and morphological characteristics in particular cellular substructures of the first non-zero concentration of diseased live biological cells;

inputting the second set of images into the trained machine-learning model to obtain a second set of embeddings representing positional and morphological characteristics in particular cellular substructures of the second non-zero concentration of diseased live biological cells;

generating a disease model based on the first set of embeddings and the second set of embeddings; and

modeling a progression of the disease based on the disease model.

15. A non-transitory computer-readable storage medium storing one or more programs for modeling a progression of a disease of interest having a plurality of disease states, the one or more programs comprising instructions, which when executed by one or more processors of an

electronic device having a display, cause the electronic device to perform operations comprising:

obtaining a first set of images captured at a first plurality of time points of a first non-zero concentration of diseased live biological cells expressing a first disease state of the disease;

obtaining a second set of images captured at a second plurality of time points of a second non-zero concentration of diseased live biological cells expressing a second disease state of the disease;

inputting the first set of images into a trained machine-learning model to obtain a first set of embeddings representing positional and morphological characteristics in particular cellular substructures of the first non-zero concentration of diseased live biological cells;

inputting the second set of images into the trained machine-learning model to obtain a second set of embeddings representing positional and morphological characteristics in particular cellular substructures of the second non-zero concentration of diseased live biological cells;

generating a disease model based on the first set of embeddings and the second set of embeddings; and

modeling a progression of the disease based on the disease model.

16. A system for modeling a characteristic of interest of a cell culture comprising one or more live mammalian cells, comprising:

one or more processors;

a memory; and

one or more programs, wherein the one or more programs are stored in the memory and configured to be executed by the one or more processors to:

obtain a first set of one or more images capturing the cell culture at a first time point;

input the first set of one or more images into a trained machine-learning model to obtain a first set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;

evaluate the characteristic of interest of the cell culture corresponding to the first time point based on the first set of embedding vectors to obtain a first set of one or more values;

obtain a second set of one or more images capturing the cell culture at a second time point;

input the second set of one or more images into the trained machine-learning model to obtain a second set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;

evaluate the characteristic of interest of the cell culture corresponding to the second time point based on the second set of embedding vectors to obtain a second set of one or more values; and

determine, from the first set of one or more values and the second set of one or more values, a change of the characteristic of interest in the cell culture.

17. The system according to claim 16, wherein the characteristic of interest is cell proliferation of the cell culture, wherein:

- i) the first set of one or more values indicates a predicted first proliferation level;
- ii) the second set of one or more values indicates a predicted second proliferation level; and
- iii) a rate of proliferation of the cell culture is determined from the predicted first proliferation level and the predicted second proliferation level.

18. The system according to claim 17, wherein the one or more programs, when executed by the one or more processors, cause the system to:
one of:

determine the in vitro and/or metabolic fitness of the cell culture based on the predicted first proliferation level and the predicted second proliferation level;

compare the rate of proliferation to a predefined threshold, optionally based upon the rate of proliferation being determined to exceed the predefined threshold

determine that the rate of proliferation is an abnormal proliferation rate and terminate growth of the cell culture before a predefined endpoint of cell growth;

predict a confluence of the cell culture for a third time point after the second time point based on the rate of proliferation of the cell culture, optionally determine timing for passaging of the cell culture based on the predicted confluence of the cell culture; or

determine timing for passaging of the cell culture based on the rate of proliferation.

19. The system according to claim 17, wherein:
the trained machine-learning model is a first machine-learning model and predicting a cell proliferation level comprises inputting the first set of embedding vectors into a second machine-learning model to obtain the cell proliferation level corresponding to the first time point and inputting the second set of embedding vectors into the second machine-learning model to obtain the cell proliferation level corresponding to the second time point;
optionally wherein
- (i) the one or more programs further include instructions to generate a time trend based on the predicted first cell proliferation level and the predicted second cell proliferation level;
 - (ii) the second machine-learning model is a linear regression classifier; or
 - (iii) the second machine-learning model is trained using a set of embedding vectors and a corresponding set of cell proliferation levels.
20. The system according to claim 17, wherein
one of:
the characteristic of interest is health of the cell culture where the first set of one or more values indicates a predicted first cell health level, the second set of one or more values indicates a predicted second cell health level, and a change of the health level of the cell culture is determined from the predicted first cell health level and the predicted second cell health level; or
the characteristic of interest is development of the cell culture where the first set of one or more values indicates a predicted first cell development level, the second set of one or more values indicates a predicted second cell development level, and a change of the development level of the cell culture is determined from the predicted first cell development level and the predicted second cell development level.
21. The system according to claim 17, wherein
one of:
the first set of one or more of images and the second set of one or more images comprise phase images;

the first set of one or more of images and the second set of one or more images are generated from fluorescence images or autofluorescence images;

the trained machine-learning model is a self-supervised machine-learning model;

the trained machine-learning model is trained using unlabeled images of biological samples;

the one or more live biological cells are healthy cells;

the one or more live biological cells are diseased cells; or

the one or more programs further include instructions to prior to obtaining a first set of one or more images apply a perturbation and/or a therapeutic agent to the cell culture, optionally wherein the perturbation and/or the therapeutic agent is a chemical treatment, a genetic treatment, or any combination thereof.

22. A non-transitory computer-readable storage medium storing one or more programs for modeling a characteristic of interest of a cell culture comprising one or more live mammalian cells, the one or more programs comprising instructions, which when executed by one or more processors of an electronic device having a display, cause the electronic device to perform operations comprising:

obtaining a first set of one or more images capturing the cell culture at a first time point;

inputting the first set of one or more images into a trained machine-learning model to obtain a first set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;

evaluating the characteristic of interest of the cell culture corresponding to the first time point based on the first set of embedding vectors to obtain a first set of one or more values;

obtaining a second set of one or more images capturing the cell culture at a second time point;

inputting the second set one or more images into the trained machine-learning model to obtain a second set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;

evaluating the characteristic of interest of the cell culture corresponding to the second time point based on the second set of embedding vectors to obtain a second set of one or more values; and

determining, from the first set of one or more values and the second set of one or more values, a change of the characteristic of interest in the cell culture.

23. A method of modeling a characteristic of interest of a cell culture comprising one or more live mammalian cells, comprising:

- obtaining a first set of one or more images capturing the cell culture at a first time point;
- inputting the first set of one or more images into a trained machine-learning model to obtain a first set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;
- evaluating the characteristic of interest of the cell culture corresponding to the first time point based on the first set of embedding vectors to obtain a first set of one or more values;
- obtaining a second set of one or more images capturing the cell culture at a second time point;
- inputting the second set one or more images into the trained machine-learning model to obtain a second set of embedding vectors representing positional and morphological characteristics in particular cellular substructures of the cell culture;
- evaluating the characteristic of interest of the cell culture corresponding to the second time point based on the second set of embedding vectors to obtain a second set of one or more values; and
- determining, from the first set of one or more values and the second set of one or more values, a change of the characteristic of interest in the cell culture.

24. A system for identifying one or more cell culture conditions for progressing one or more live biological cells towards a desired cell state, the system comprising:

- one or more processors;
- a memory; and
- one or more programs, wherein the one or mom programs are stored in the memory and configured to be executed by the one or more processors to:
 - perform a plurality of cell culture condition identification cycles on the one or more live biological cells until a condition is met, wherein each cell culture condition identification cycle comprises:
 - obtaining a set of one or more images capturing the one or more live biological cells;
 - determining, from at least a subset of the set of one or more images, a cell state of the one or more live biological cells;
 - identifying a new cell culture condition for progressing the one or more live biological cells towards the desired cell state, by inputting the cell state and the desired cell state into a trained machine-learning model, wherein

the trained machine-learning model is an active-learning machine-learning model; and

applying the new cell culture condition to the one or more live biological cells;

prompting a user to provide one or more user inputs about a state of the one or more live biological cells after the new cell culture condition is applied; and

retraining the active-learning machine-learning model based on the user inputs; and

identify the one or more cell culture conditions, based on outcomes of the plurality of cell culture condition identification cycles, for use in progressing live biological cells towards the desired cell state in future cell cultures.

25. The system of claim 24, wherein

the one or more live biological cells are a first set of one or more live biological cells that are deposited in a first well, and the plurality of cell culture condition identification cycles is a first plurality of cell culture condition identification cycles; and

the one or more programs further include instructions to:

deposit a second set of one or more live biological cells in a second well;

perform a second plurality of cell culture condition identification cycles on the second set of one or more live biological cells, wherein the second plurality of cell culture condition identification cycles is different from the first plurality of cell culture condition identification cycles; and

prioritize one or more cell culture conditions in the first plurality of cell culture condition identification cycles and the second plurality of cell culture condition identification cycles based on the outcomes of the first plurality of cell culture condition identification cycles and the second plurality of cell culture condition identification cycles.

26. The system according to claim 25, wherein

one of:

a time frame for performing the first plurality of cell culture condition identification cycles overlaps with the time frame for performing the second plurality of cell culture condition identification cycles;

the first well and the second well belong to the same multi-well plate; or

wherein differences between the first plurality of cell culture condition identification cycles and the second plurality of cell culture condition identification cycles

comprise cell culture medium ingredient differences, cell culture temperature differences, cell culture pressure exposure differences, and/or cell culture medium light exposure differences.

27. The system according to claim 24, wherein one of:

- the condition is met when the desired cell state is achieved;
- the condition is met when a predefined number of cell culture condition identification cycles are performed;
- the user is an individual;
- the set of one or more images comprise phase images;
- the set of one or more images are generated based on fluorescence images or autofluorescence images;
- the one or more live biological cells are induced pluripotent stem cells, optionally wherein the desired cell state is a non-pluripotent cell state; or
- the one or more live biological cells are healthy cells, optionally wherein the desired cell state is a diseased cell state.

28. The system according to claim 24, wherein one of:

- the new cell culture condition is a perturbagen, optionally wherein the perturbagen is a chemical treatment, a genetic treatment, or any combination thereof;
- the new cell culture condition is a therapeutic agent, optionally wherein the therapeutic agent is at least one of a chemical treatment, a genetic treatment and combination thereof;
- the new cell culture condition is a temperature, pressure, and/or light exposure;
- applying a new type of cell culture condition to the one or more live biological cells is automated by one or more electronic devices; or
- the one or more live biological cells are mammalian cells.

29. A non-transitory computer-readable storage medium storing one or more programs for identifying one or more cell culture conditions for progressing one or more live biological cells towards a desired cell state, the one or more programs comprising instructions, which when

executed by one or more processors of an electronic device having a display, cause the electronic device to perform operations comprising:

performing a plurality of cell culture condition identification cycles on the one or more live biological cells until a condition is met, wherein each cell culture condition identification cycle comprises:

- obtaining a set of one or more images capturing the one or more live biological cells;
- determining, from at least a subset of the set of one or more images, a cell state of the one or more live biological cells;
- identifying a new cell culture condition for progressing the one or more live biological cells towards the desired cell state, by inputting the cell state and the desired cell state into a trained machine-learning model, wherein the trained machine-learning model is an active-learning machine-learning model; and
- applying the new cell culture condition to the one or more live biological cells;

prompting a user to provide one or more user inputs about a state of the one or more live biological cells after the new cell culture condition is applied; and

retraining the active-learning machine-learning model based on the user inputs; and

identifying the one or more cell culture conditions, based on outcomes of the plurality of cell culture condition identification cycles, for use in progressing live biological cells towards the desired cell state in future cell cultures.

30. A method for identifying one or more cell culture conditions for progressing one or more live biological cells towards a desired cell state, comprising:

performing a plurality of cell culture condition identification cycles on one or more live biological cells until a condition is met, wherein each cell culture condition identification cycle comprises:

- obtaining a set of one or more images capturing the one or more live biological cells;
- determining, from at least a subset of the set of one or more images, a cell state of the one or more live biological cells;
- identifying a new cell culture condition for progressing the one or more live biological cells towards a desired cell state, by inputting the cell state and the desired cell state into a trained machine-learning model, wherein the trained machine-learning model is an active-learning machine-learning model;
- applying the new cell culture condition to the one or more live biological cells;

prompting a user to provide one or more inputs about a state of the one or more live biological cells after the new cell culture condition is applied;
retraining the active-learning machine-learning model based on the user inputs; and
identifying the one or more cell culture conditions, based on outcomes of the plurality of cell culture condition identification cycles, for use in progressing live biological cells towards the desired cell state in future cell cultures.