WHAT IS CLAIMED IS:

1. A method comprising

preparing a substrate for imaging to establish location and registration of biochemical sites on the substrate;

detecting field spots corresponding to biochemical sites in an image on the substrate;

aligning a two-dimensional grid with field spots of biochemical sites on the substrate to determine a grid offset; and

registering said grid points to known positions in a field, the registering step including cross correlating the field spots with a first known deletion pattern of field spots on the substrate to determine absolute location within a field.

2. The method according to claim 1, the deletion pattern being selected to be pseudo random.

3. The method of claim 1, the registering step comprising further cross correlating the field spots with a second known deletion pattern identifying location of the field spots on the substrate.

4. The method of claim 1, the aligning step comprising iteratively testing different combinations of rotation, scale, x-offset, and y-offset to find a tested combination having minimum least squares distances between each grid point and each field spot in the pattern of field spots.

5. The method of claim 1, the alignment step including:

collecting field spots by intensity group;

plotting group average spot brightness versus group average distance from nearest grid points; and

repeating the fine fitting step on all spots in groups for which the group average distance from the nearest grid point is less than a threshold value.

6. A method comprising:

providing a solid, planar substrate having an array of sites on which biochemical experiments are performed, the array characterized by a periodic distance between adjacent sites;

observing light emitted by the biochemical experiments using an imaging system having an array of pixels, the array characterized by a constant distances between pixels;

light emitted by the biochemical experiments being focused in spots on the array of pixels, each said spot corresponding to a biochemical experiment; and

distance between said spots not being an integer multiple of distance between said pixels.

7. The method of Claim 6, the biochemical experiments comprising combinatorial probe – anchor ligation with DNA nanoballs.

8. A device comprising:

a solid, planar substrate having discrete optically resolvable surface sites, said surface sites being modified to support biochemical experiments;

wherein said surface sites are located at spots in a two-dimensional periodic array of spots on a surface of the substrate; and

wherein a fraction of the spots that would otherwise exist stand deleted from the array according to at least one known deletion pattern.

9. The device of claim 8, the deletion pattern being pseudo random.

10. The device of claim 8, the fraction being between approximately 1% and approximately 3%.

11. The device of claim 8, the biochemical experiments comprising combinatorial probe – anchor ligation with DNA nanoballs.

12. A method comprising:

providing a solid, planar substrate having discrete surface sites, the surface sites being modified to support biochemical experiments, the sites being located at spots in a two-dimensional periodic array of spots on a surface of the substrate, and a fraction of the spots that would otherwise exist being deleted from the array according to a known deletion pattern;

performing biochemical experiments at the sites;

obtaining images of the biochemical experiments;

cross-correlating the image with the deletion pattern to determine absolute location of the spots; and

observing the images with subpixel accuracy to extract information about the biochemical experiments.

13. The method of Claim 12, the image observing step comprising weighting contributions of output from adjacent pixels based on exact location of the spots.

14. A system comprising:

means for preparing a substrate for imaging to establish location and registration of biochemical sites on the substrate;

means for detecting field spots corresponding to biochemical sites in an image on a substrate;

means for aligning field spots to grid points of a two-dimensional grid; and

means for registering said grid points to known positions in said field; the registering step including cross correlating the grid points with a known deletion pattern of field spots on the substrate to determine absolute location.

What is claimed is:

1. A method comprising preparing a planar two-dimensional substrate for imaging to establish location and registration of biochemical sites on the substrate by providing a predetermined two-dimensional pattern of biochemical sites on the substrate; detecting image field spots in a spatial two-dimensional array on the substrate corresponding to biochemical sites in an image on the substrate; aligning a spatial two-dimensional grid with image field spots of biochemical sites on the substrate to determine a grid offset; and registering said grid points to known positions in a spatial two-dimensional field, the registering step including cross correlating the image field spots with a first known spatial two-dimensional image deletion pattern of image field spots on the substrate to determine absolute location within a field.

2. The method according to claim 1, the deletion pattern in the periodic spatial pattern being selected to be pseudo random.

3. The method of claim 1, the registering step comprising further cross correlating the image field spots with a second known image deletion pattern identifying location of the image field spots on the substrate.

4. The method of claim 1, the preparing step comprising subtracting a background light level from the image.

5. The method of claim 4, the subtracting step including: finding intensity of the dimmest pixel within a defined array of pixels; and subtracting that intensity from each pixel the defined array.

6. The method of claim 1, the image field spots detecting step including choosing the location of a brightest pixel associated with each field spot.

7. The method of claim 1, the aligning step comprising a coarse fitting and a fine fitting.

8. The method of claim 1, the aligning step comprising iteratively testing different combinations of rotation, scale, x-offset, and y-offset to find a tested combination having minimum least squares distances between each grid point and each field spot in the pattern of field spots.

9. The method of claim 1, the aligning step further comprising: forming the sum of the squared distances between each image field spot and its corresponding grid point; and finding the minimum of the sum by: calculating its partial derivatives with respect to rotation, scale, x-offset, and y-offset variables, setting the partial derivatives equal to zero, and solving the resulting system of linear equations.

10. The method of claim 1, the alignment step including: collecting image field spots by intensity group; plotting group average spot brightness versus group average distance from nearest grid points; and repeating the fine fitting step on all image field spots in groups for which the group average distance from the nearest grid point is less than a threshold value.

11. A device comprising: a solid, planar substrate having discrete optically resolvable surface sites arranged according to a predetermined array pattern, said surface sites being modified to support biochemical experiments; wherein said surface sites are located at image field spots in a predetermined spatial two-dimensional periodic array of spots on a surface of the substrate; and wherein a fraction of the image field spots

that would otherwise exist stand deleted from the array according to at least one known spatial two-dimensional deletion pattern.

12. The device of claim 11, the deletion pattern in the two-dimensional periodic array being pseudo random.

13. The device of claim 11, the fraction being between approximately 1% and approximately 3%.

14. The device of claim 11, the array having at least one million spots.

15. The device of claim 11, wherein only said surface sites of the substrate support biochemical experiments.

16. The device of claim 11, areas of the substrate other than said surface sites being chemically treated to reduce non-specific binding of biomolecules.

17. The device of claim 11, the biochemical experiments comprising combinatorial probe-anchor ligation with DNA nanoballs.

18. A method comprising: providing a solid, planar substrate having discrete surface sites, the surface sites being modified to support biochemical experiments, the sites being located at spots in a predetermined spatial two-dimensional periodic array of spots on a surface of the substrate, and a fraction of the spots that would otherwise exist being deleted from the array according to a known deletion pattern; performing biochemical experiments at the sites; obtaining images of the biochemical experiments at the sites; cross-correlating the image with the deletion pattern to determine absolute location of the spots; and observing the images with subpixel accuracy to extract information about the biochemical experiments.

19. The method of claim 18, the image observing step comprising weighting contributions of output from adjacent pixels based on exact location of the spots.

20. The method of claim 18, the deletion pattern being pseudo random.

21. The method of claim 18 wherein the fraction is between approximately 1% and approximately 3%.

22. The method of claim 18, wherein only said surface sites of the substrate support biochemical experiments.

23. The method of claim 18, areas of the substrate other than said surface sites being chemically treated to reduce non-specific binding of biomolecules.

24. The method of claim 18, the biochemical experiments comprising combinatorial probe-anchor ligation with DNA nanoballs.

25. The method according to claim 1, wherein the imaging steps are configured to interact with a plurality of different fluorescent labels on molecules at each one of the biochemical sites, the preparing step including: obtaining at least one fluorescence-specific image of the substrate for further processing of image data.

26. The method of claim 1, the cross-correlating comprising interacting with a pattern having less than three

percent of deleted grid points.

27. A system comprising: a preprocessor for preparing a planar substrate for imaging to establish location and registration of biochemical sites on the substrate according to a predetermined spatial two-dimensional pattern; a detector for detecting image field spots in the spatial two-dimensional pattern corresponding to biochemical sites in an image on the substrate; a first subsystem for aligning a spatial two-dimensional grid with said image field spots; and a second subsystem for registering grid points with said image field spots; the registering subsystem including a first cross correlator for cross correlating the image field spots with a first known deletion pattern of image field spots on the substrate to determine absolute location within a two-dimensional field.

28. The system of claim 27, the second subsystem including a second cross correlator for cross correlating the image field spots with a second known deletion pattern identifying absolute location of the field spots on the substrate.

29. The system of claim 28, at least the first known deletion pattern being pseudo random.