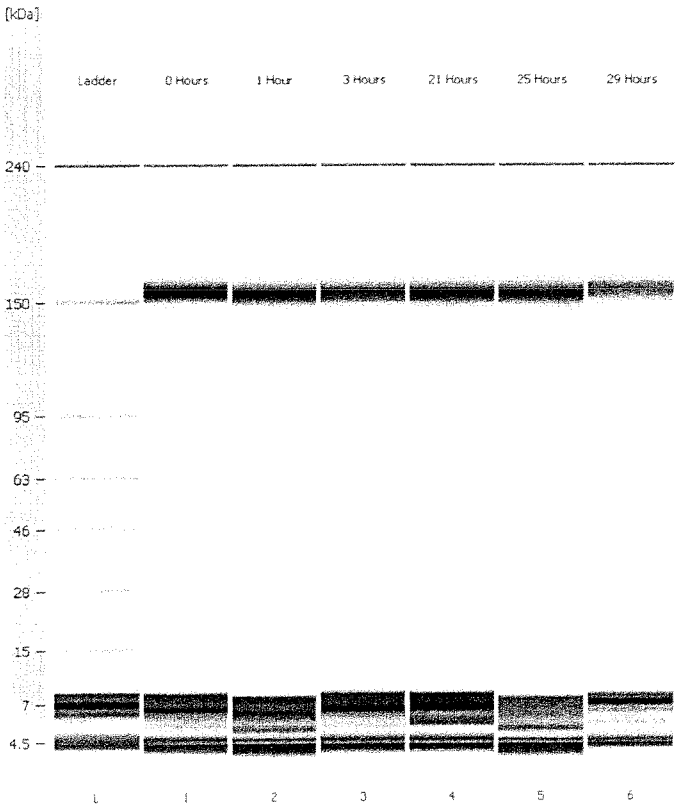


Figure 1. **Dialysis Experiment:** Digital gel-like imaging obtained from Bioanalyzer analysis showing that ocrelizumab inside the diaslysis bag remained intact during the incubation period.

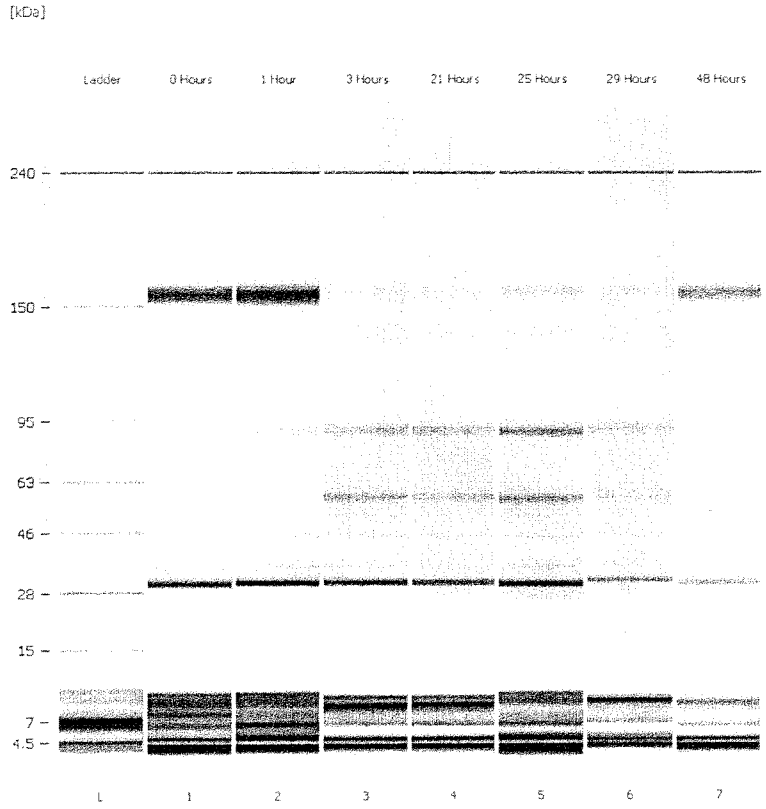


Figure 2. **Dialysis Experiment:** Digital gel-like imaging obtained from Bioanalyzer analysis showing that ocrelizumab outside the diaslysis bag was reduced during the incubation period as evidenced by the loss of intact antibody (~ 150 kDa) and the formation of antibody fragments. At 48-hour time point (Lane 7), the reduced antibody appeared to be reoxdized presumably as a result of losing reduction activity in the HCCF. The band appearing just above the 28 kDa marker is arising from the light chain of antibody. There was a significant amount of free light already present in the HCCF before the incubation began. The presence of excess free light chain and dimers of light chain in the HCCF is typical for the cell line producing ocrelizumab.

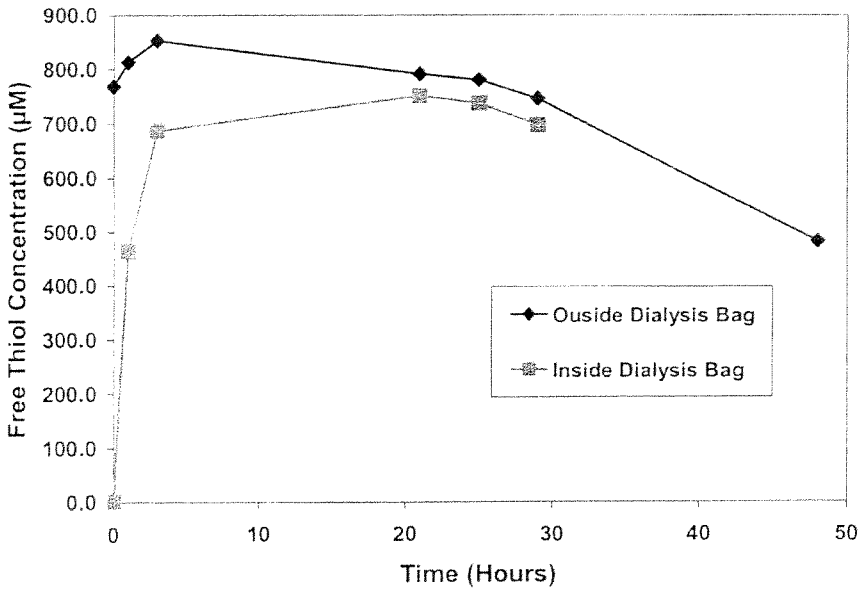


Figure 3. **Free Thiol Levels from Dialysis Experiment:** Free thiols inside ( ) and outside (♦) the dialysis bag reach comparable levels within a few hours, indicating a good exchange of small molecule components in the HCCF between inside and outside the dialysis bag.

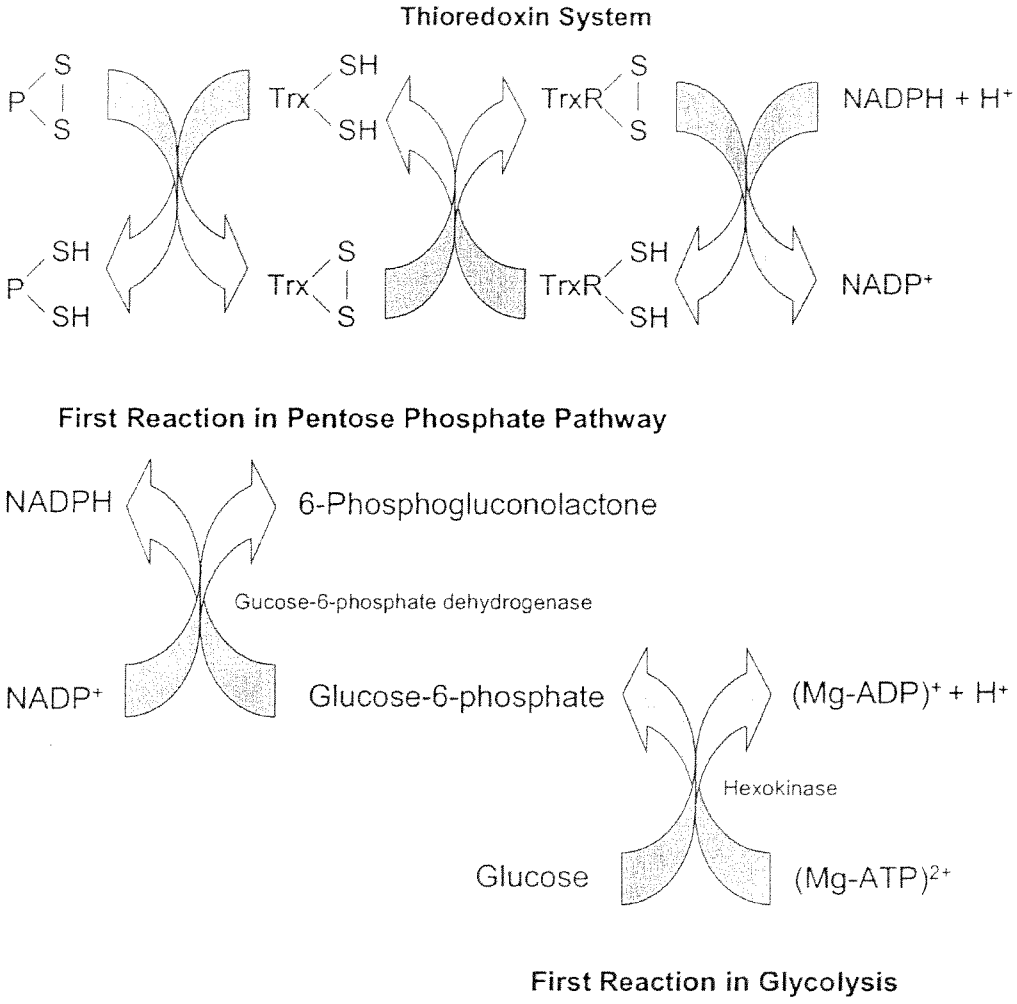


Figure 4. **Thioredoxin System and Other Reactions Involved in Antibody Reduction** : The thioredoxin system, composed of thioredoxin (Trx), thioredoxin reductase (TrxR) and NADPH, is a hydrogen donor system for reduction of disulfide bonds in proteins. Trx is a small monomeric protein with a CXXC active site motif that catalyzes many redox reactions through thiol-disulfide exchange. The oxidized Trx can be reduced by NADPH via TrxR. The reduced Trx is then able to catalyze the reduction of disulfides in proteins. The NADPH required for thioredoxin system is provided via reactions in pentose phosphate pathway and glycolysis.

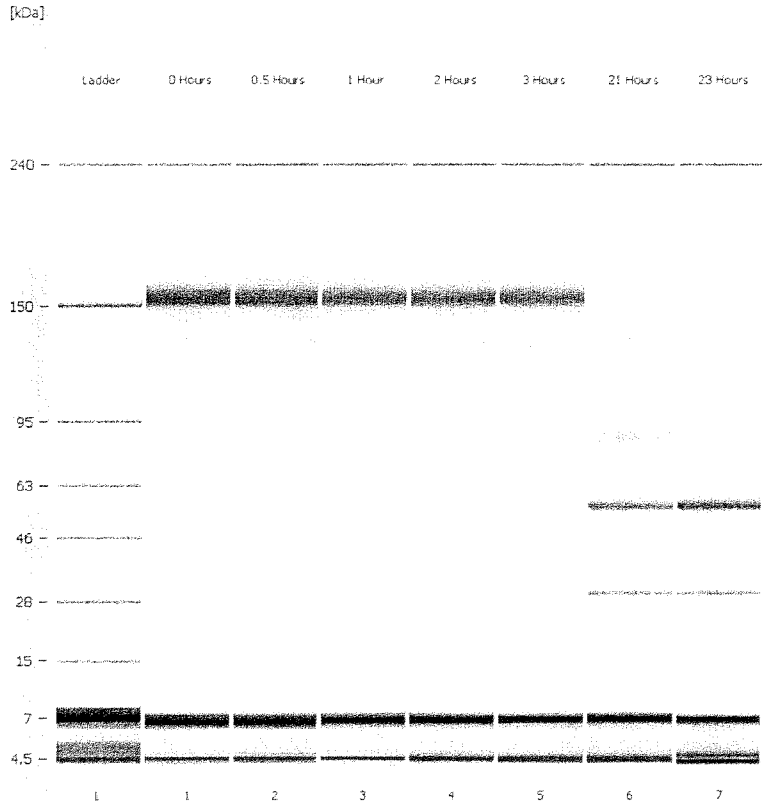


Figure 5. ***In Vitro* Activity of Thioredoxin System:** Digital gel-like image from Bioanalyzer analysis showing that incubation of intact ocrelizumab (1 mg/mL) with 0.1 μM TrxR (rat liver), 5 μM Trx (human), and 1 mM NADPH in PBS results in the reduction of ocrelizumab (completely reduced in less than 21 hours).

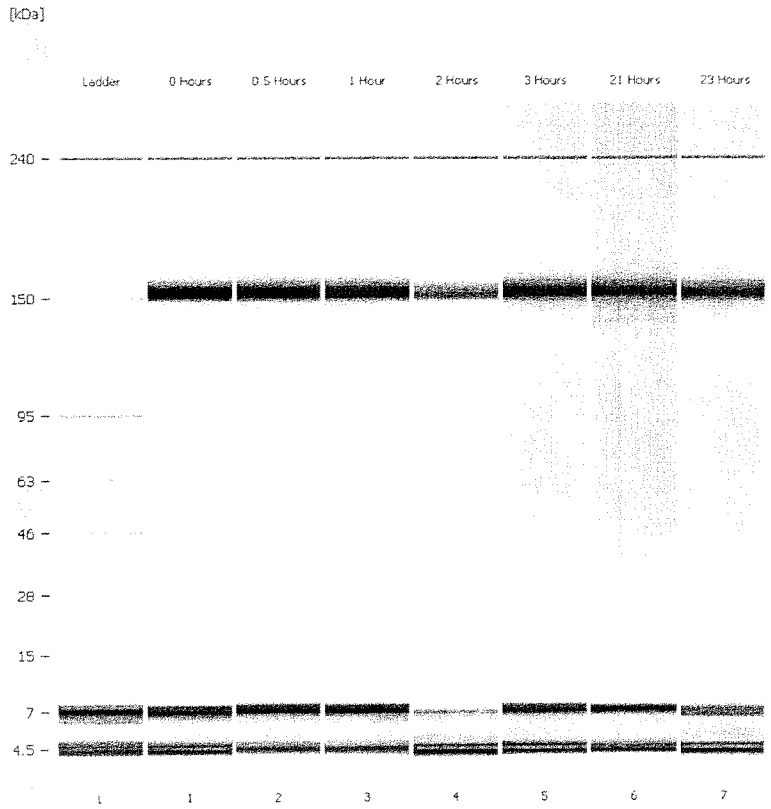


Figure 6. ***In vitro* Activity of Thioredoxin System Inhibited by Aurothioglucose:** The addition of aurothioglucose at a concentration of 1 mM to the same reaction mixture as described in the caption for Figure 5 effectively inhibits the ocrelizumab reduction as shown in the digital gel-like image from Bioanalyzer analysis.

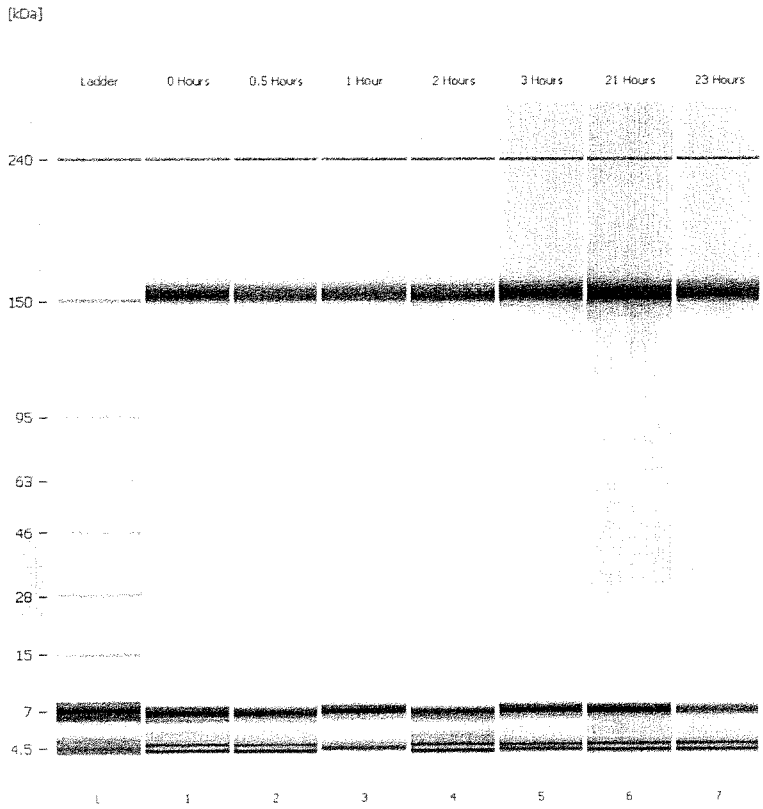


Figure 7. ***In vitro* Activity of Thioredoxin System Inhibited by Aurothiomalate:** The addition of aurothiomalate at a concentration of 1 mM to the same reaction mixture as described in the caption for Figure 5 effectively inhibits the ocrelizumab reduction as shown in the digital gel-like image from Bioanalyzer analysis.

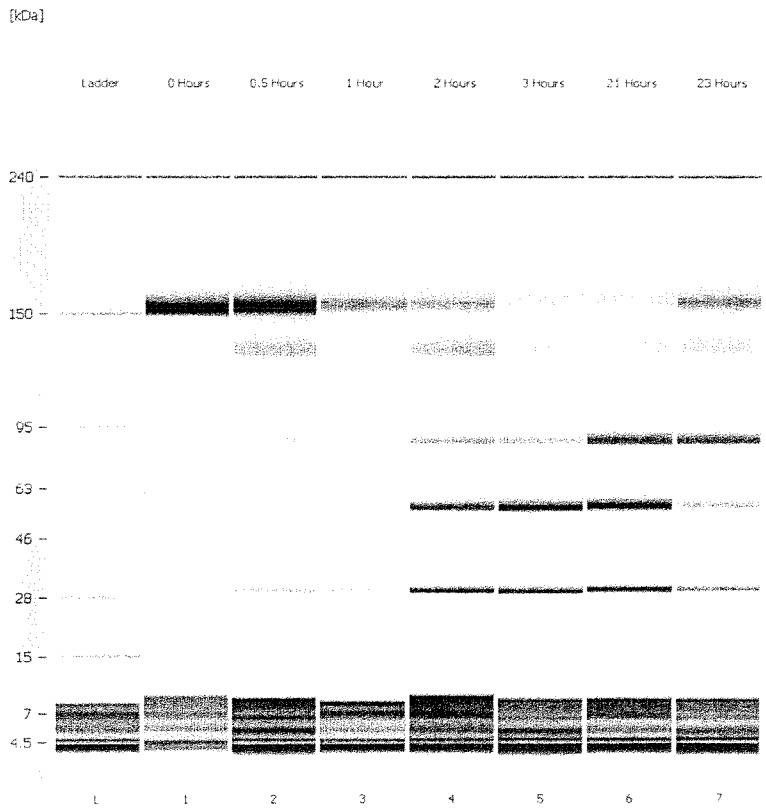


Figure 8. ***In Vitro* Activity of Thioredoxin System:** Digital gel-like image from Bioanalyzer analysis showing that incubation of intact ocrelizumab (1 mg/mL) with 0.1 μM TrxR (rat liver), 5 μM Trx (human), and 1 mM NADPH in 10 mM histidine sulfate buffer results in the reduction of ocrelizumab in less than 1 hours.

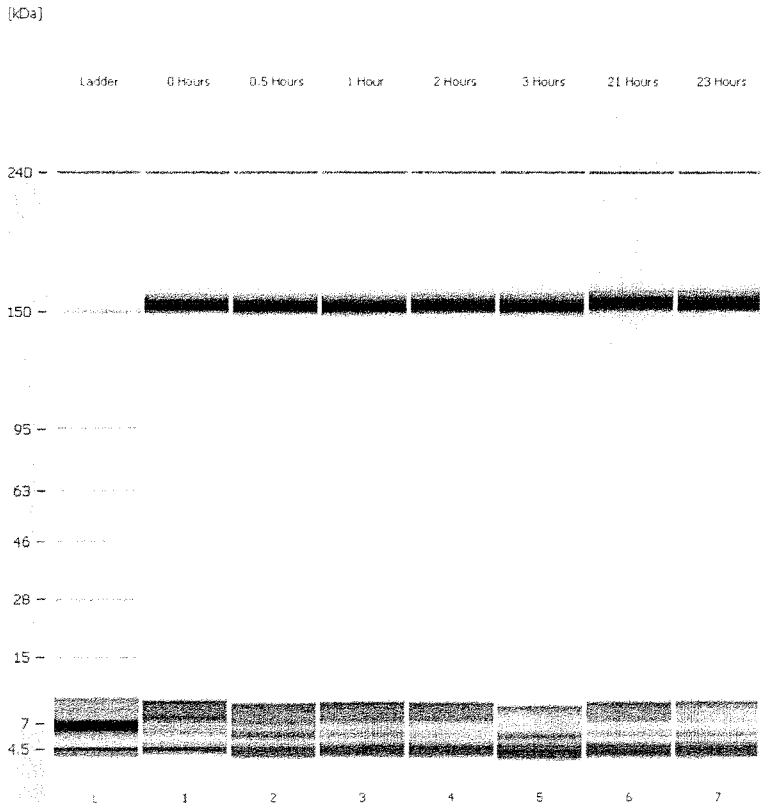


Figure 9. ***In vitro* Activity of Thioredoxin System Inhibited by $CuSO_4$:** The addition of $CuSO_4$ at a concentration of 50 μM to the same reaction mixture as described in the caption for Figure 8 effectively inhibits the ocrelizumab reduction as shown in the digital gel-like image from Bioanalyzer analysis.

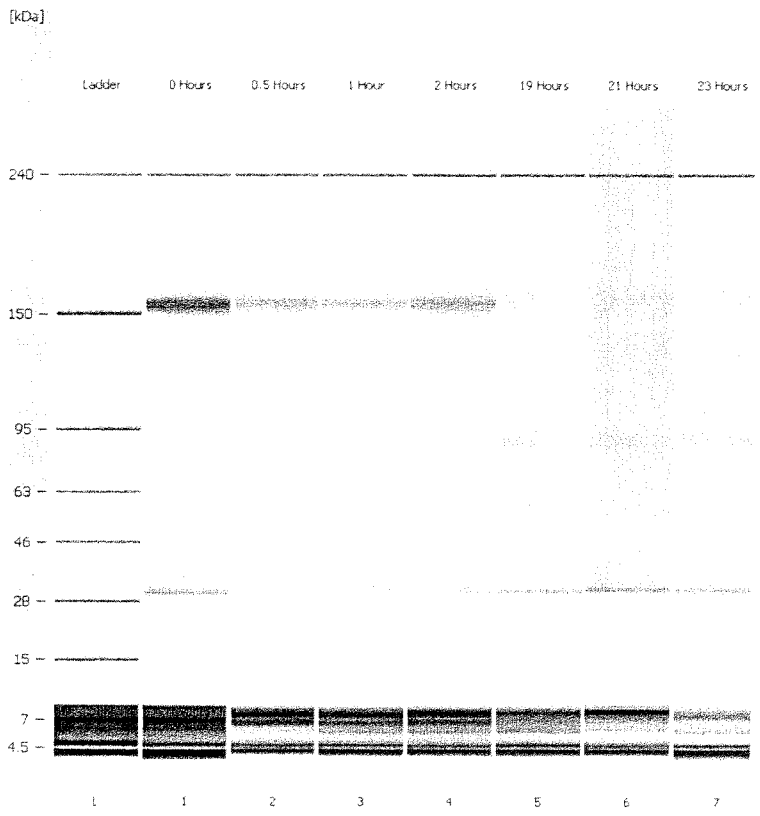


Figure 10. **Ocrelizumab Reduction:** Digital gel-like image from Bioanalyzer analysis showing that ocrelizumab is reduced in an incubation experiment using a homogenized HCCF generated from a 3-L fermentor.

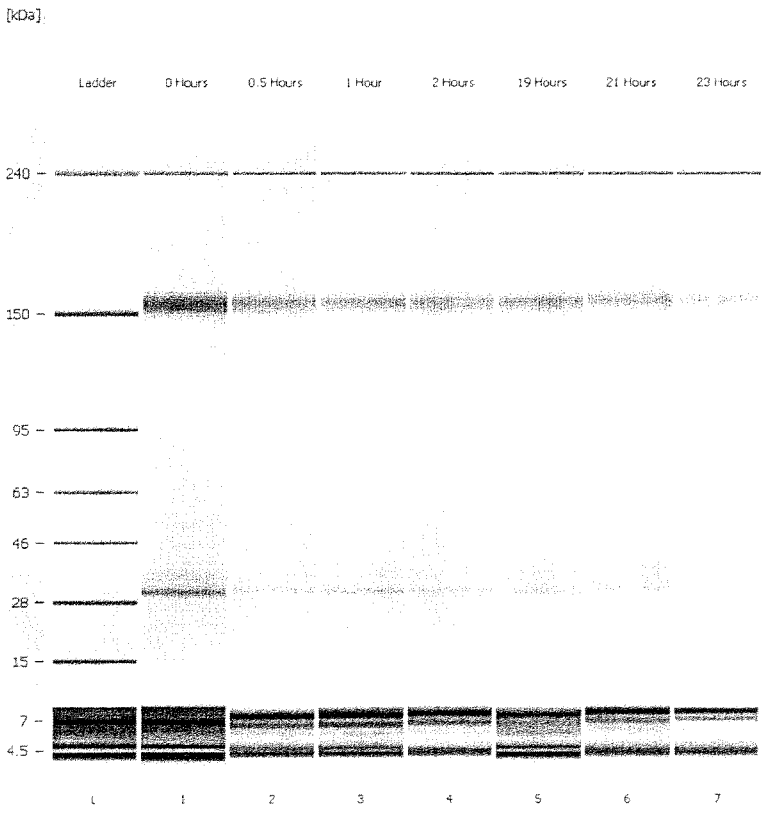


Figure 11. **Inhibition of Ocrelizumab Reduction In HCCF by Aurothioglucose:** Digital gel-like image from Bioanalyzer analysis showing that the addition of 1 mM aurothioglucose to the same HCCF as used for the incubation experiment shown in Figure 10 effectively inhibits the reduction of ocrelizumab.

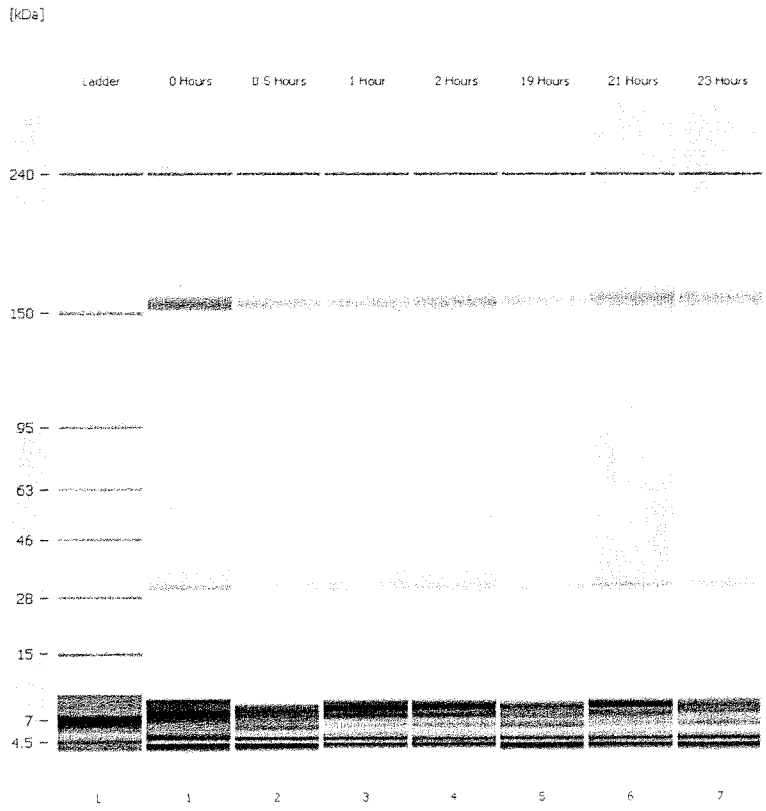


Figure 12. **Inhibition of Ocrelizumab Reduction In HCCF by Aurothiomalate:** Digital gel-like image from Bioanalyzer analysis indicating that the addition of 1 mM aurothiomalate to the same HCCF as used for the incubation experiment shown in Figure 10 effectively inhibits the reduction of ocrelizumab.

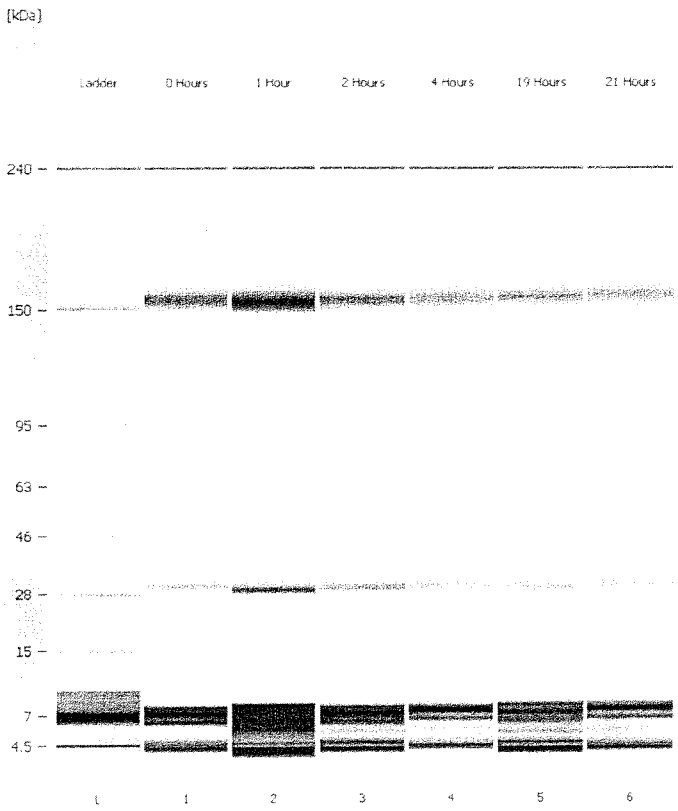


Figure 13. **Losing Reduction Activity in HCCF:** The HCCF from one of the 12 kL manufacturing runs for ocrelizumab (Run 8) that already experienced several freeze/thaw cycles was used in an incubation experiment. Surprisingly, no ocrelizumab reduction was observed in the Bioanalyzer analysis despite the antibody reduction seen previously in the freshly thawed HCCF from this same fermentation.

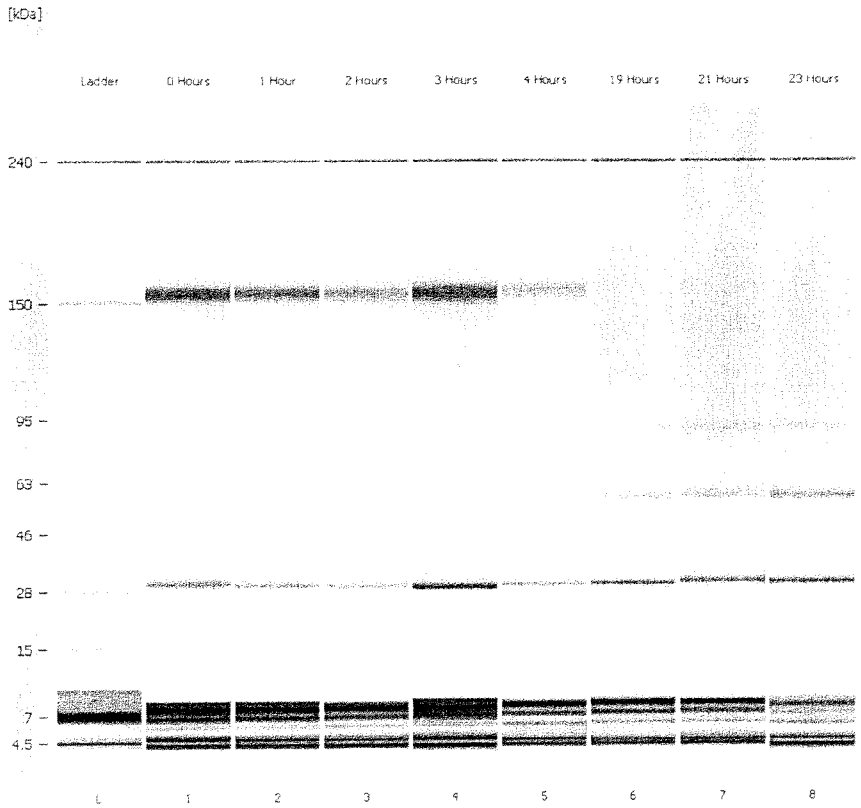


Figure 14. **The Lost Reduction Activity in HCCF Restored by Addition of NADPH:** The reduction of ocrelizumab is observed again in the Bioanalyzer assay after the addition of NADPH at a concentration of 5 mM into the HCCF whose reduction activity has been lost (see Figure 13).

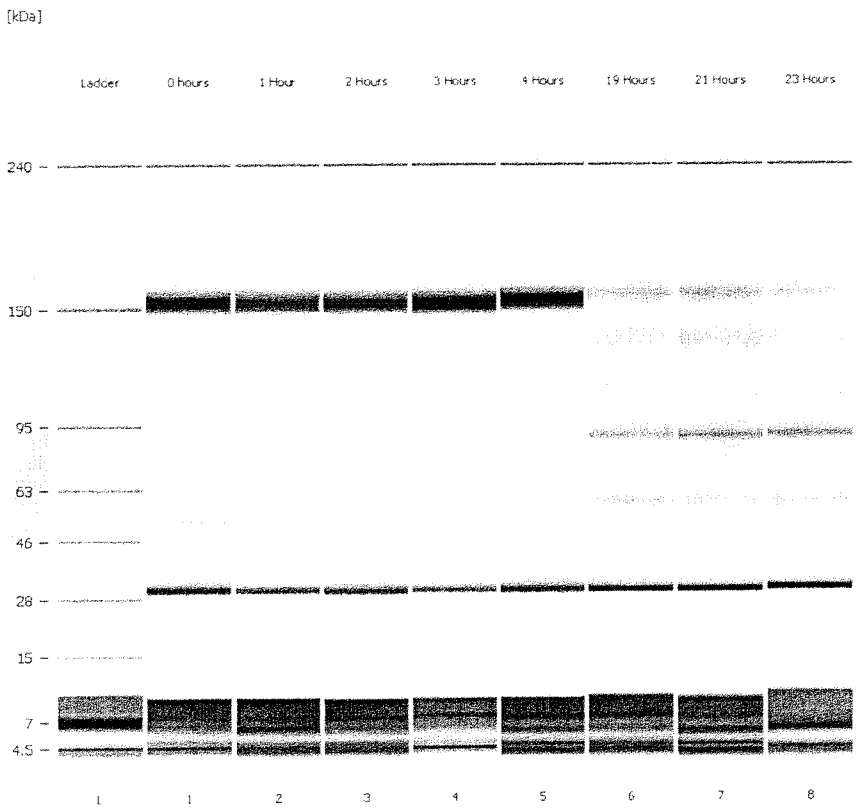


Figure 15. **The Lost Reduction Activity in HCCF Restored by Addition of Glucose-6-Phosphate:** The reduction of ocrelizumab is observed again in the Bioanalyzer assay after the addition of G6P at a concentration of 10 mM into the HCCF whose reduction activity has been lost (see Figure 13).

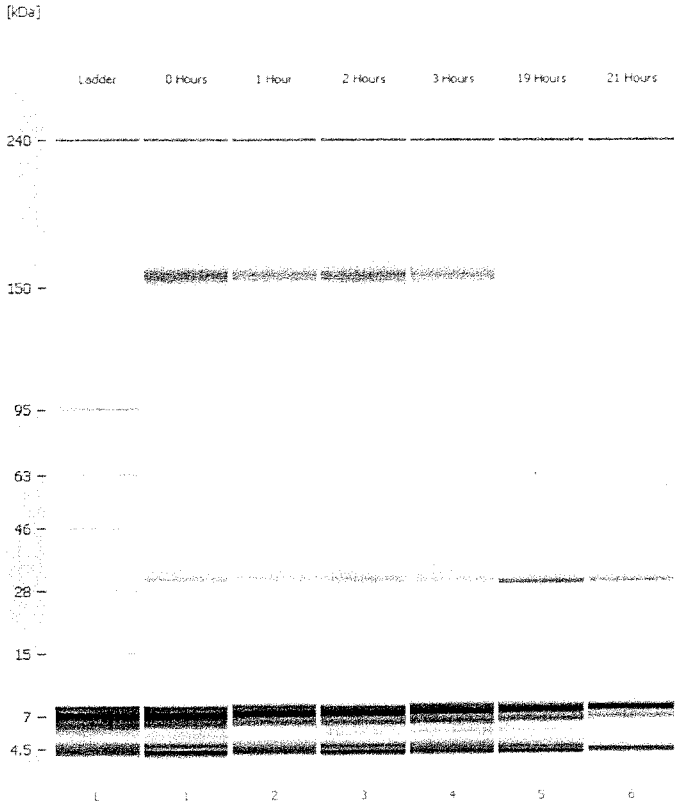


Figure 16. **Ocrelizumab Reduction:** Digital gel-like image from Bioanalyzer analysis showing that ocrelizumab is reduced in an incubation experiment using a HCCF from 12 kL Run 9.

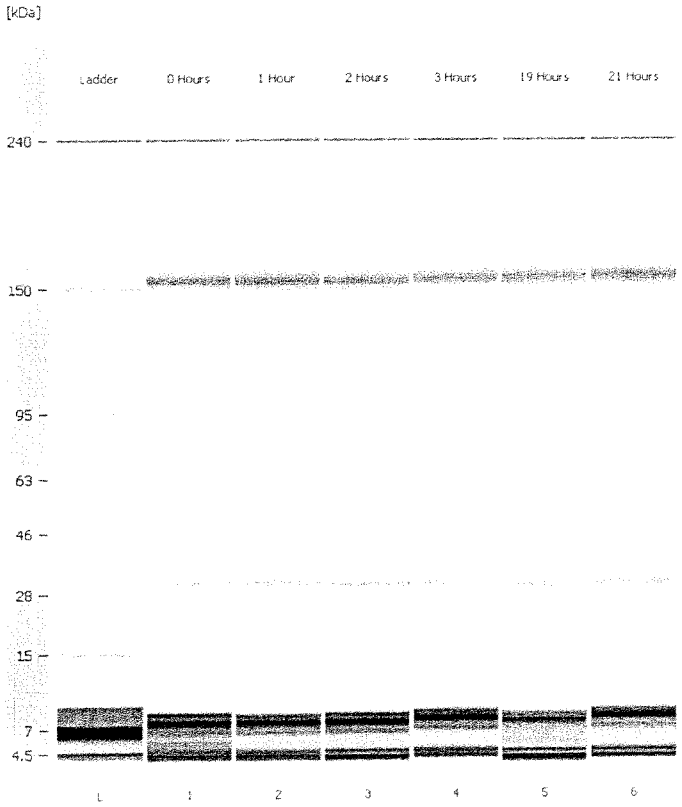


Figure 17. **EDTA Inhibits Ocrelizumab Reduction:** Digital gel-like image from Bioanalyzer analysis showing that the reduction of ocrelizumab is inhibited in an incubation experiment using a HCCF from 12 kL Run 9 with EDTA added at a concentration of 20 mM.

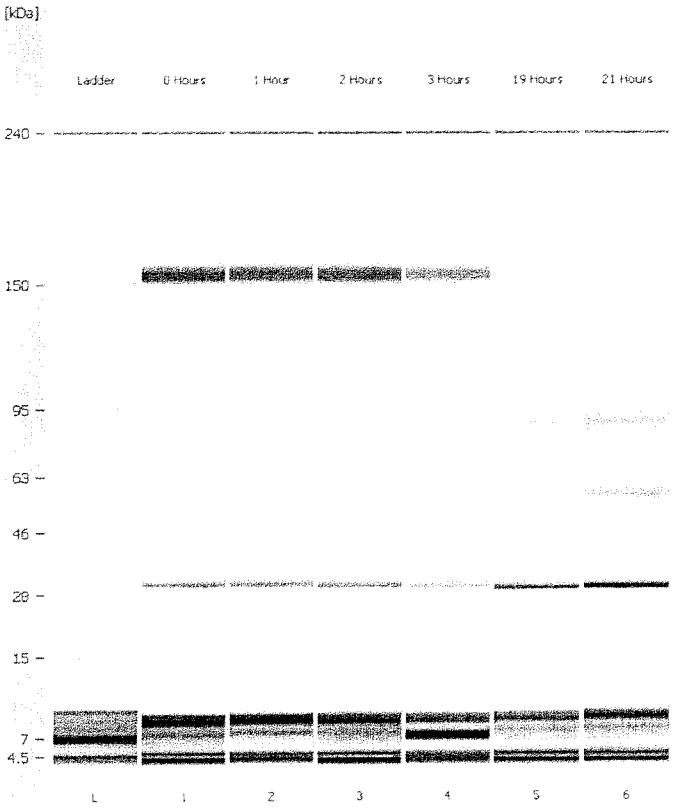


Figure 18. **The Lost Reduction Activity in Run 8 HCCF Restored by Addition of Glucose-6-Phosphate but No Inhibition of Reduction by EDTA:** The reduction of ocrelizumab is observed in the Bioanalyzer assay after the addition of G6P at a concentration of 5 mM and 20 mM EDTA into the HCCF whose reduction activity has been lost (see Figure 13). In contrast to the results shown in Figure 17, the presence of EDTA does not block the reduction of ocreliumab.

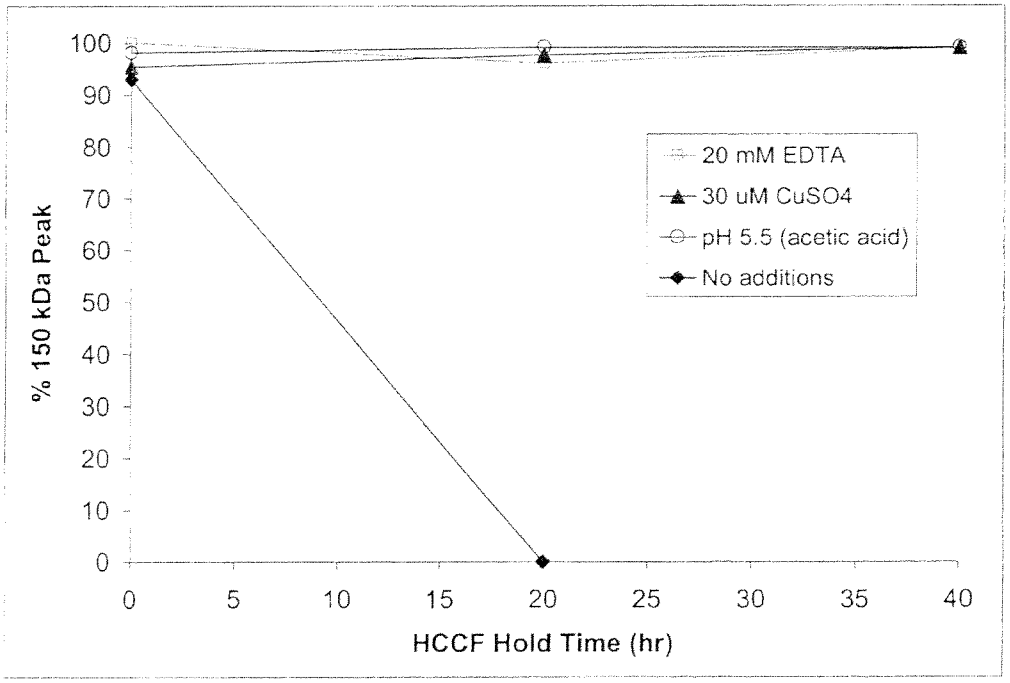


Figure 19. **Inhibition of Ocrelizumab Reduction:** Three different methods (addition of EDTA, addition of $CuSO_4$, and adjustment of pH to 5.5) are effective in inhibiting ocrelizumab reduction as demonstrate by the quantitative Bioanalyzer results showing that nearly 100% intact (150 kDa) antibody in the protein A elution pools. In contrast, ocrelizumab is completely reduced in the control HCCF after 20 hours of HCCF hold time.

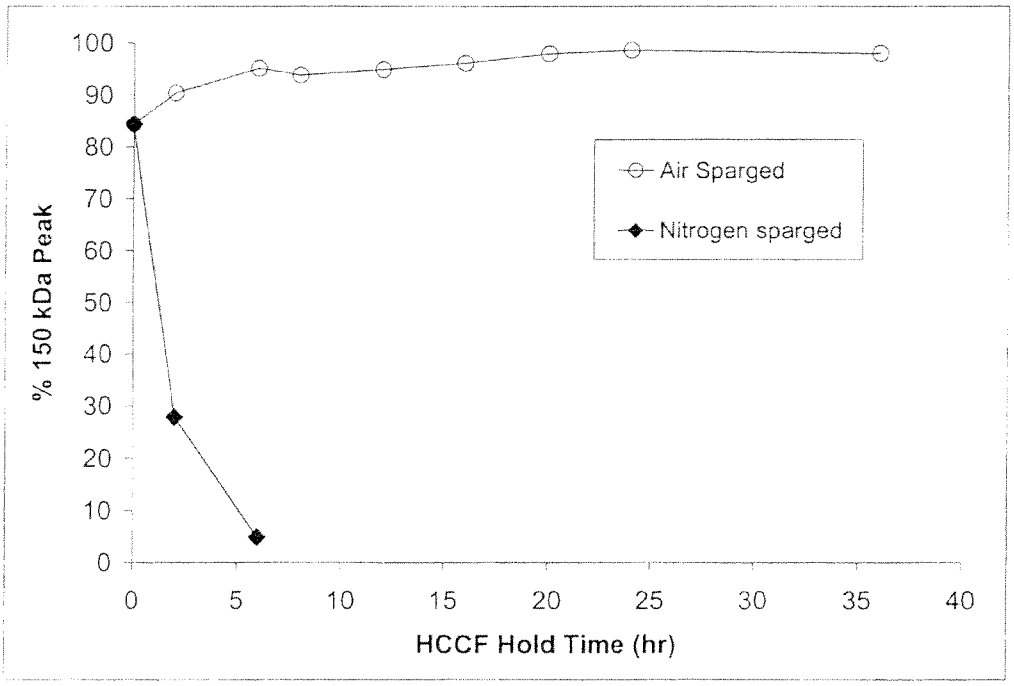


Figure 20. **Inhibition of Ocrelizumab Reduction:** Air sparing the HCCF is also effective in inhibiting ocrelizumab reduction as demonstrate by the quantitative Bioanalyzer results showing that nearly 100% intact (150 kDa) antibody in the protein A elution pools. In constrast, ocrelizumab is almost completely reduced in the control HCCF after 5 hours of sparging with nitrogen.

Light Chain

```
1               15                  30                  45
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPK

46              60                  75                  90
LLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ

91              105
HYTTPPTFGQGTKVEIK
```

Figure 21

Heavy Chain

```
1               15                  30                  45
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGL

46              60                  75                  90
EWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED

91              105                 120
TAVYYCSRWGGDGFYAMDYWGQGTLVTVSS
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Figure 22

Typical Batch or Fed-Batch Culture Process

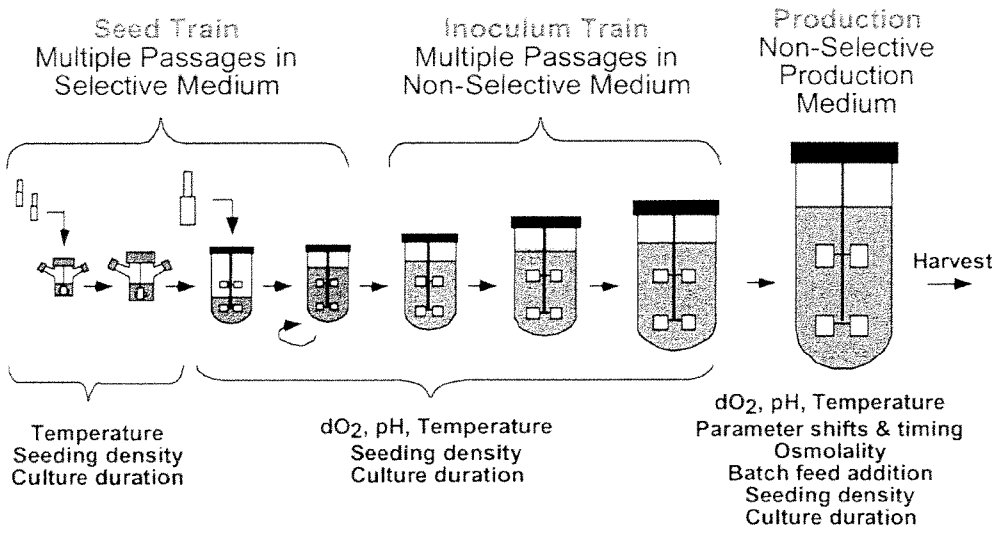


Figure 23

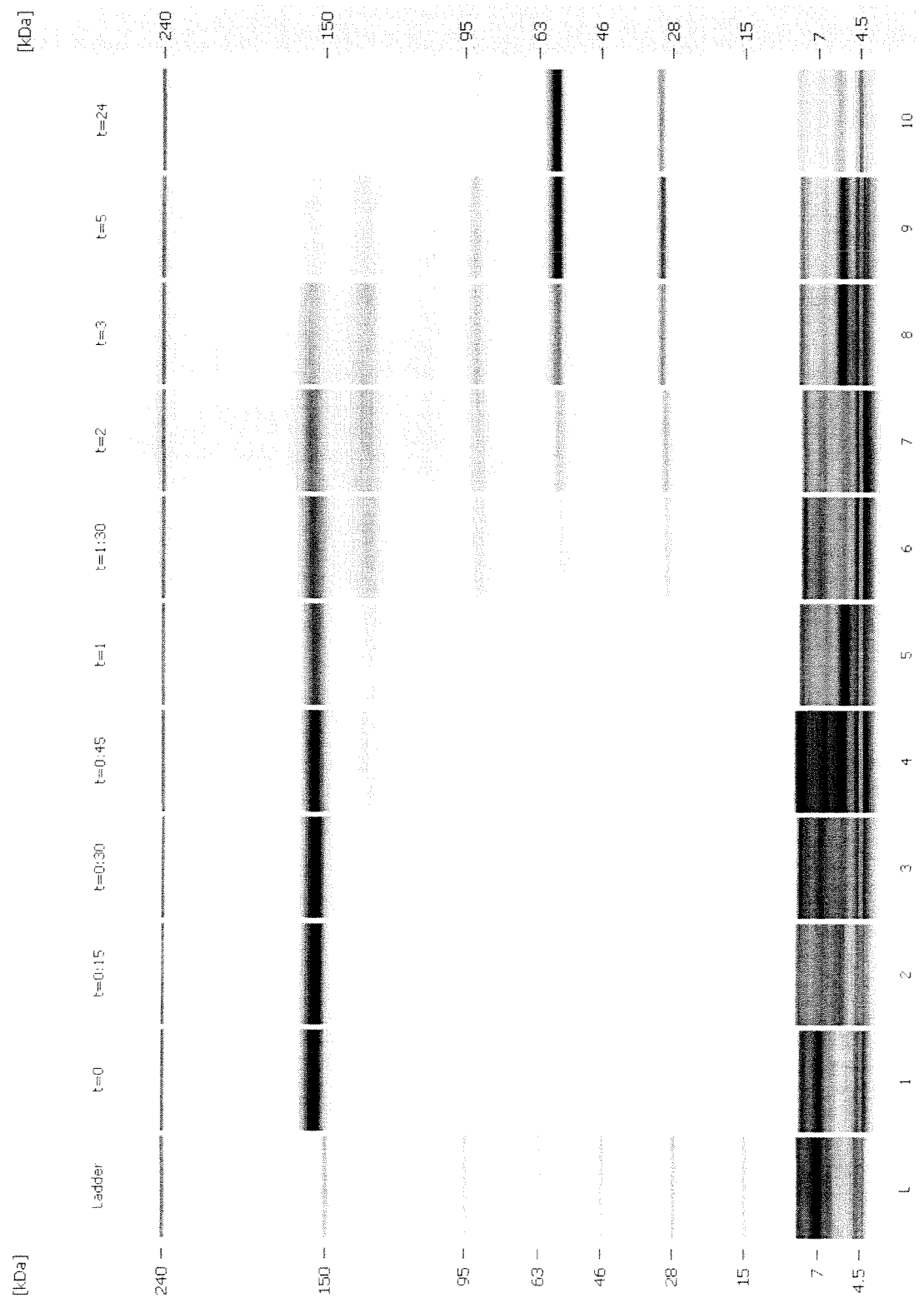

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FIG. 24

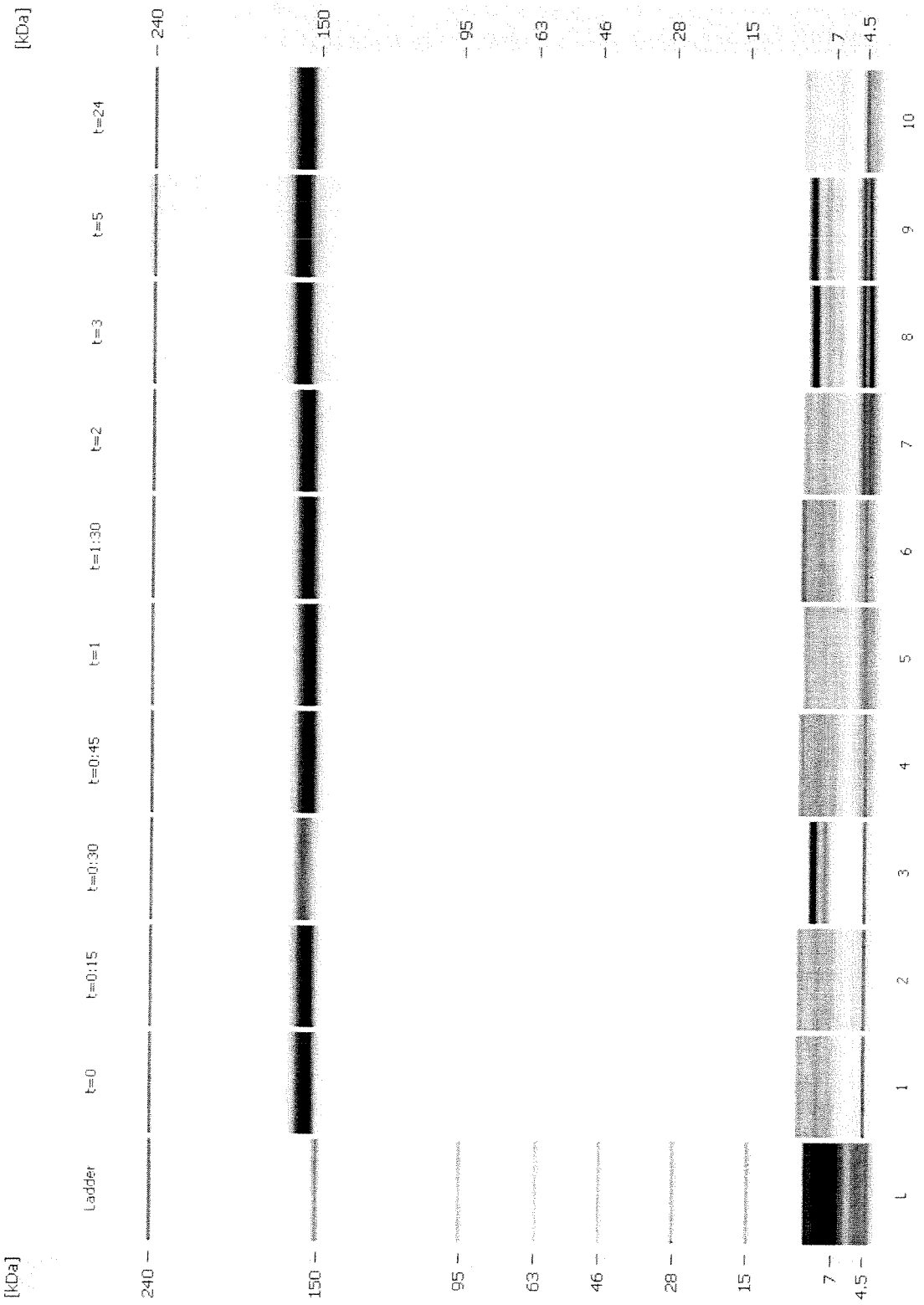

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FIG. 25

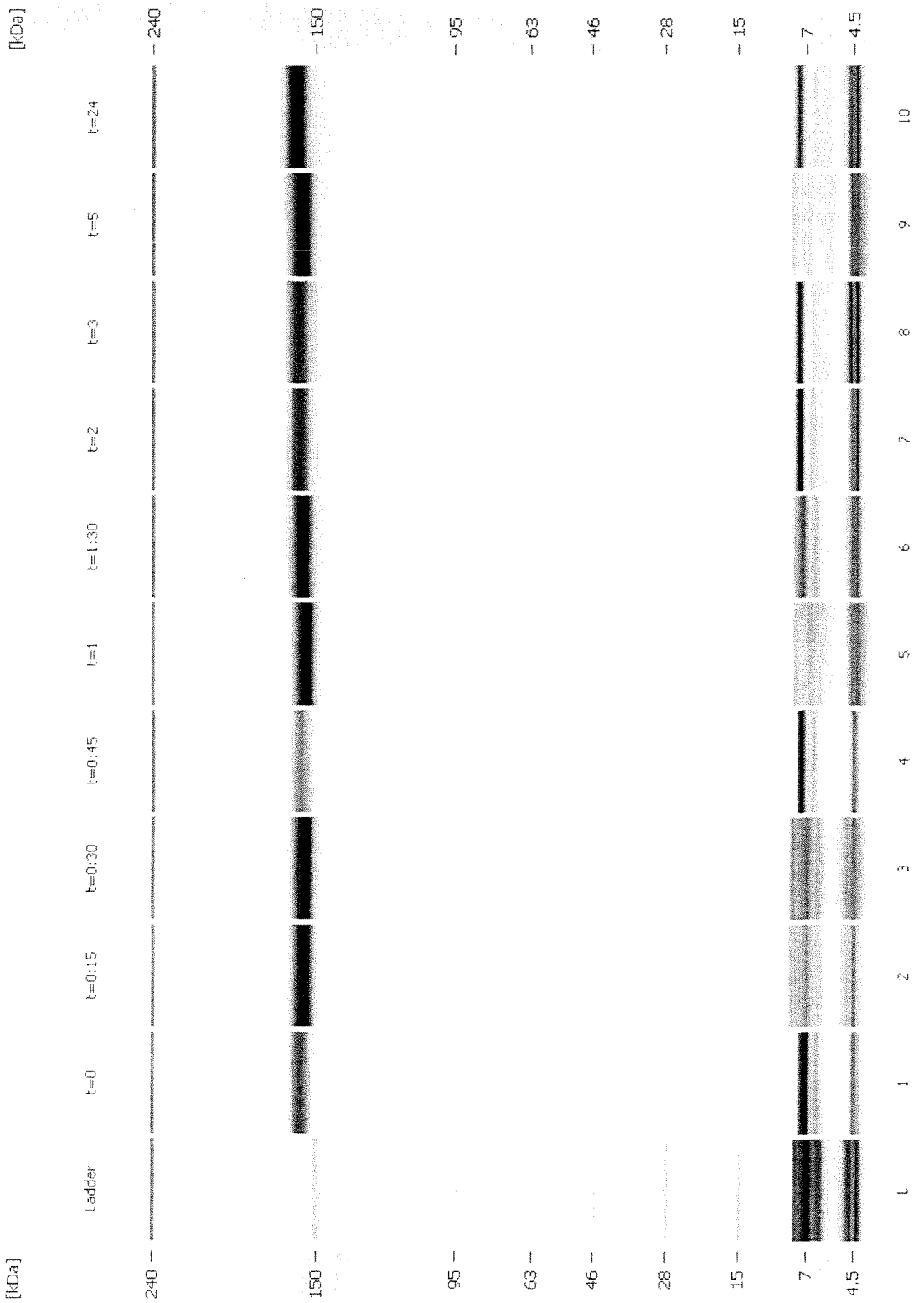

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FIG. 26

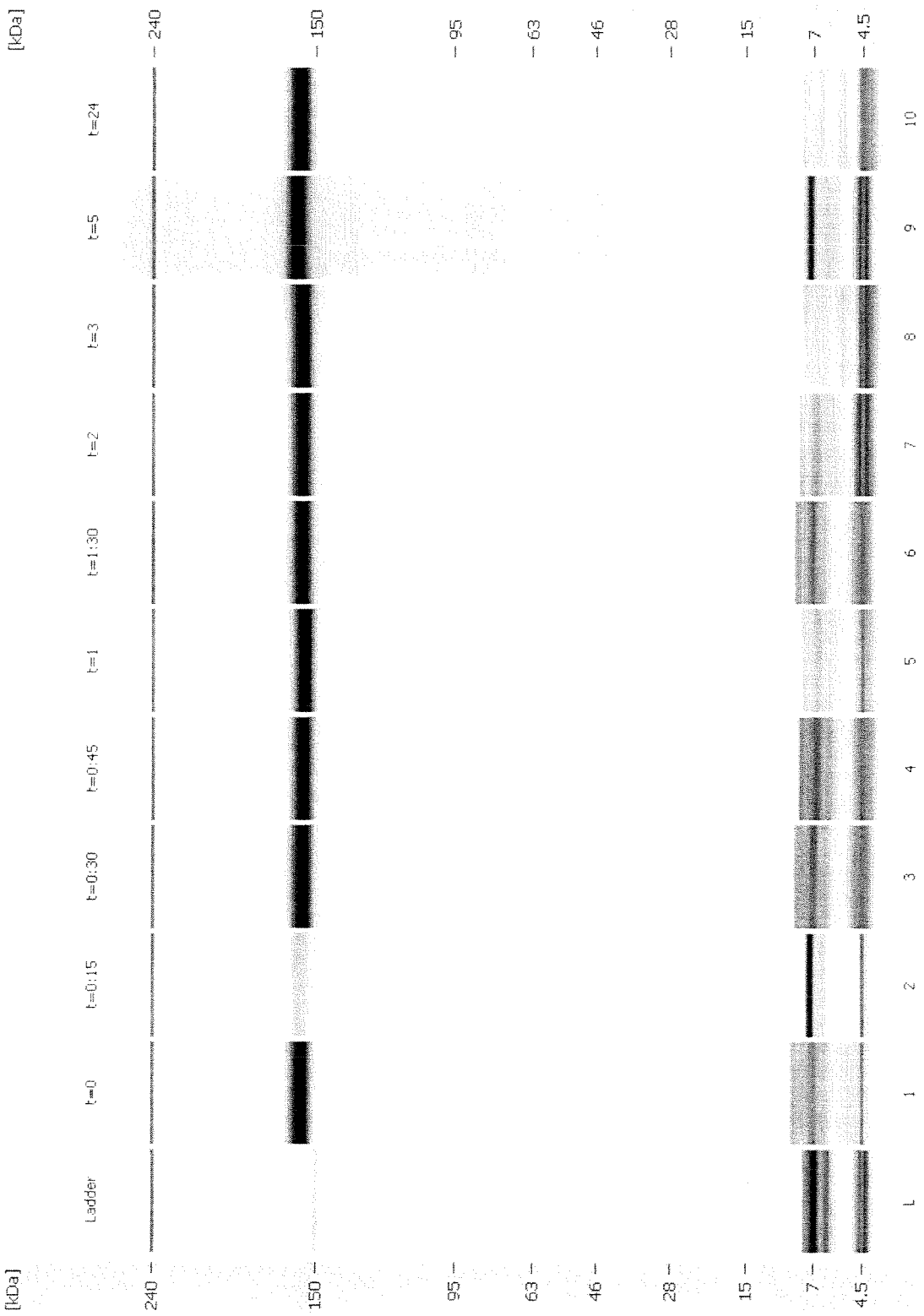

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FIG. 27

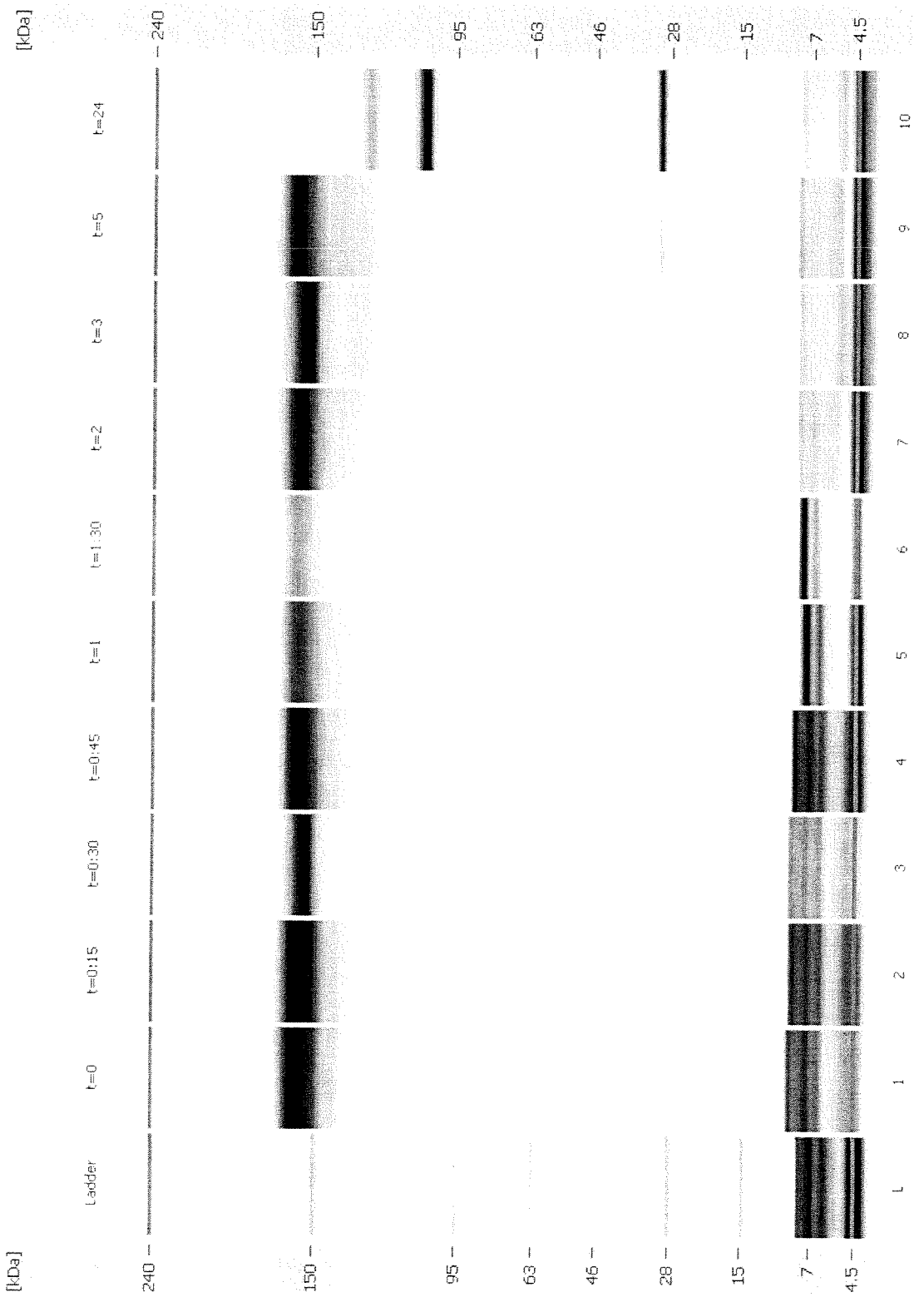

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FIG. 28

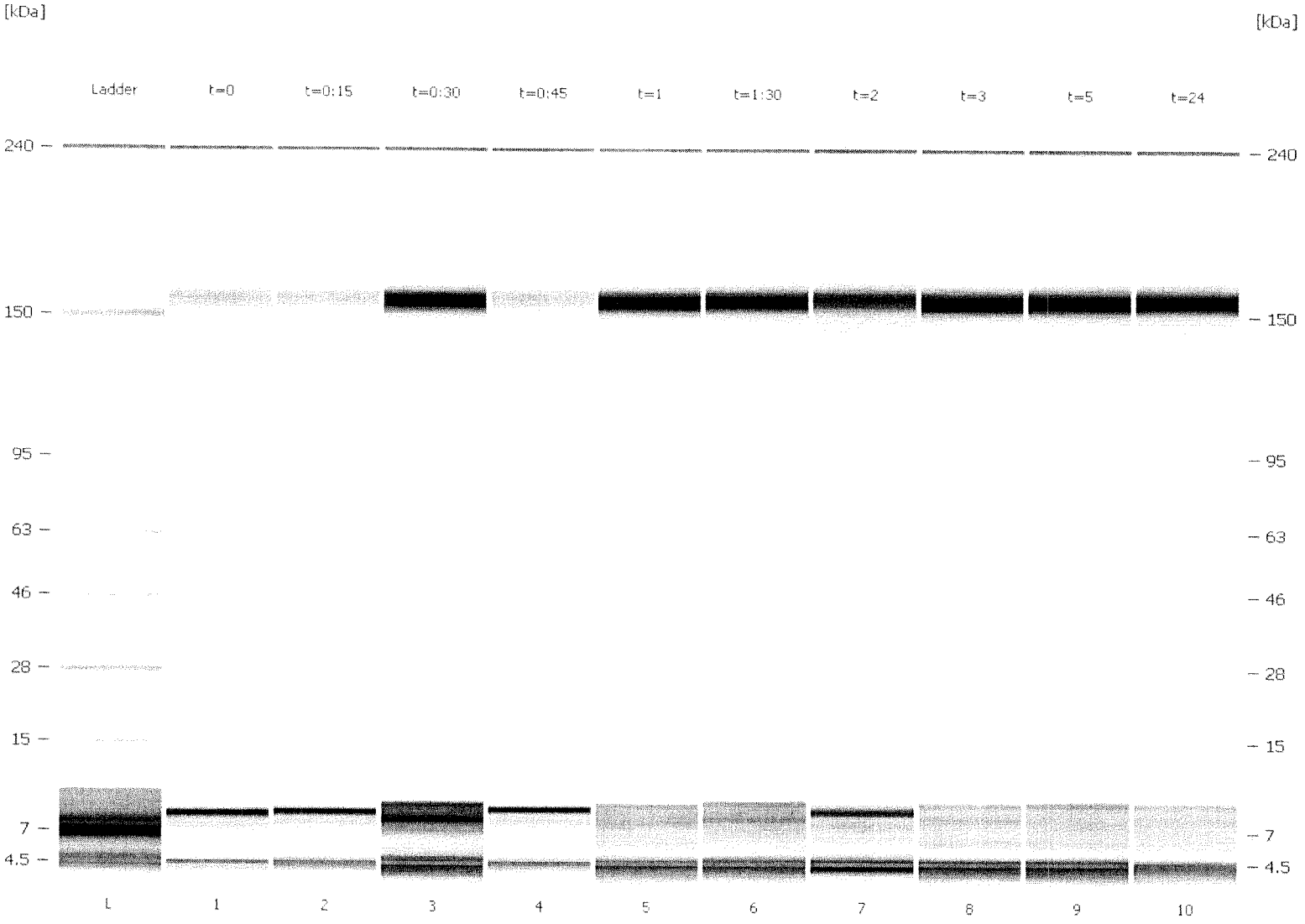

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FIG. 29

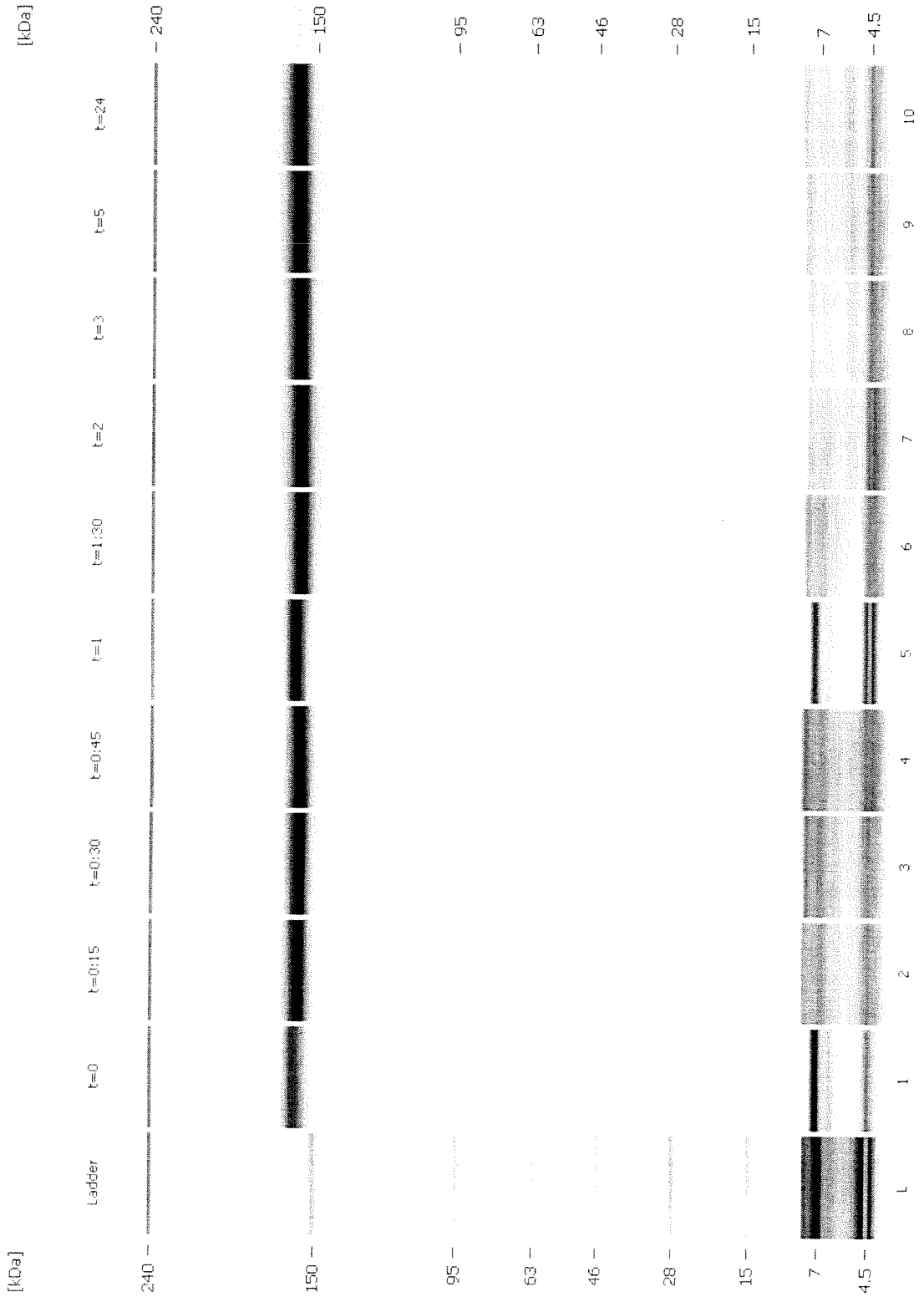

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FIG. 30

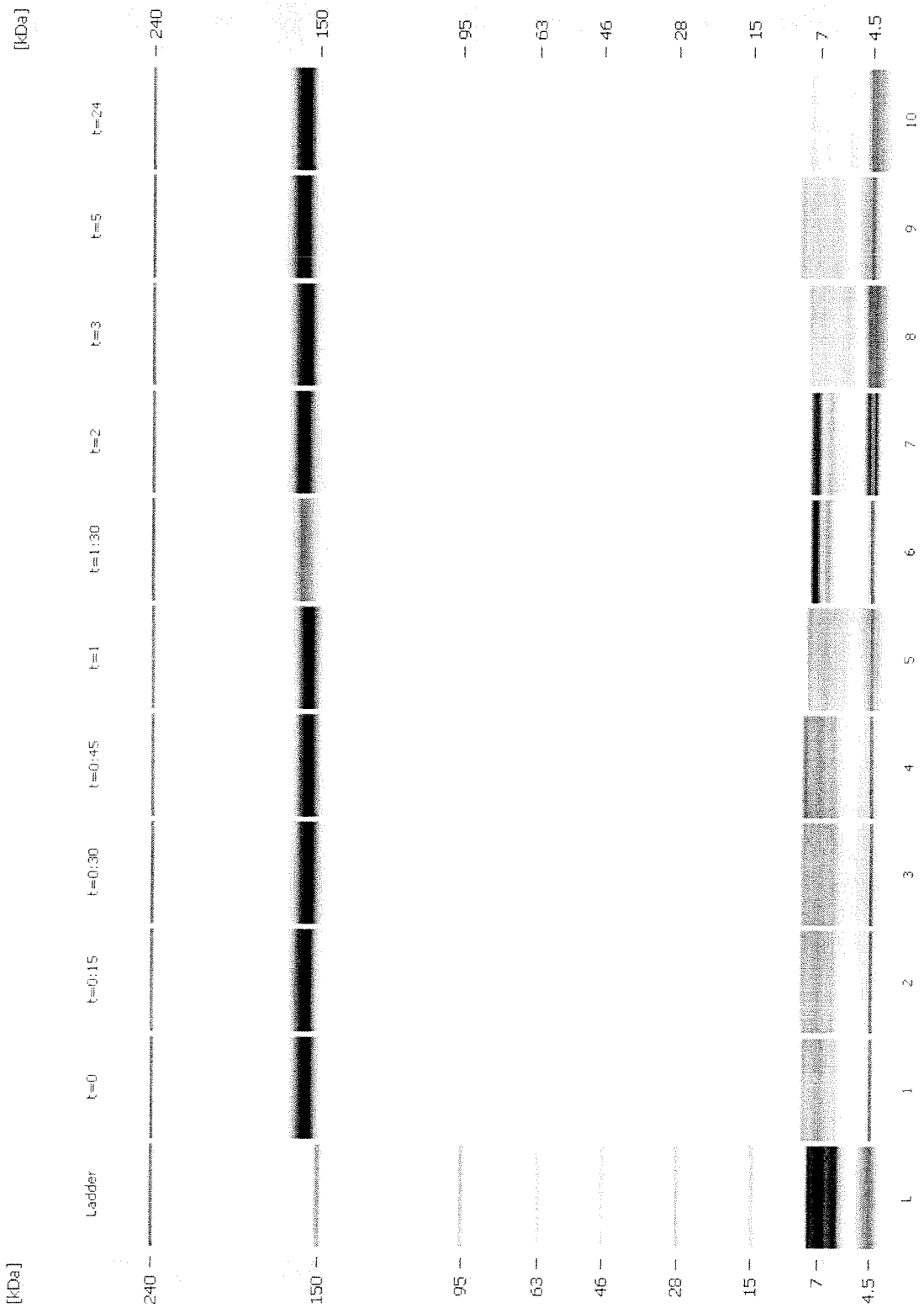

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FIG. 31

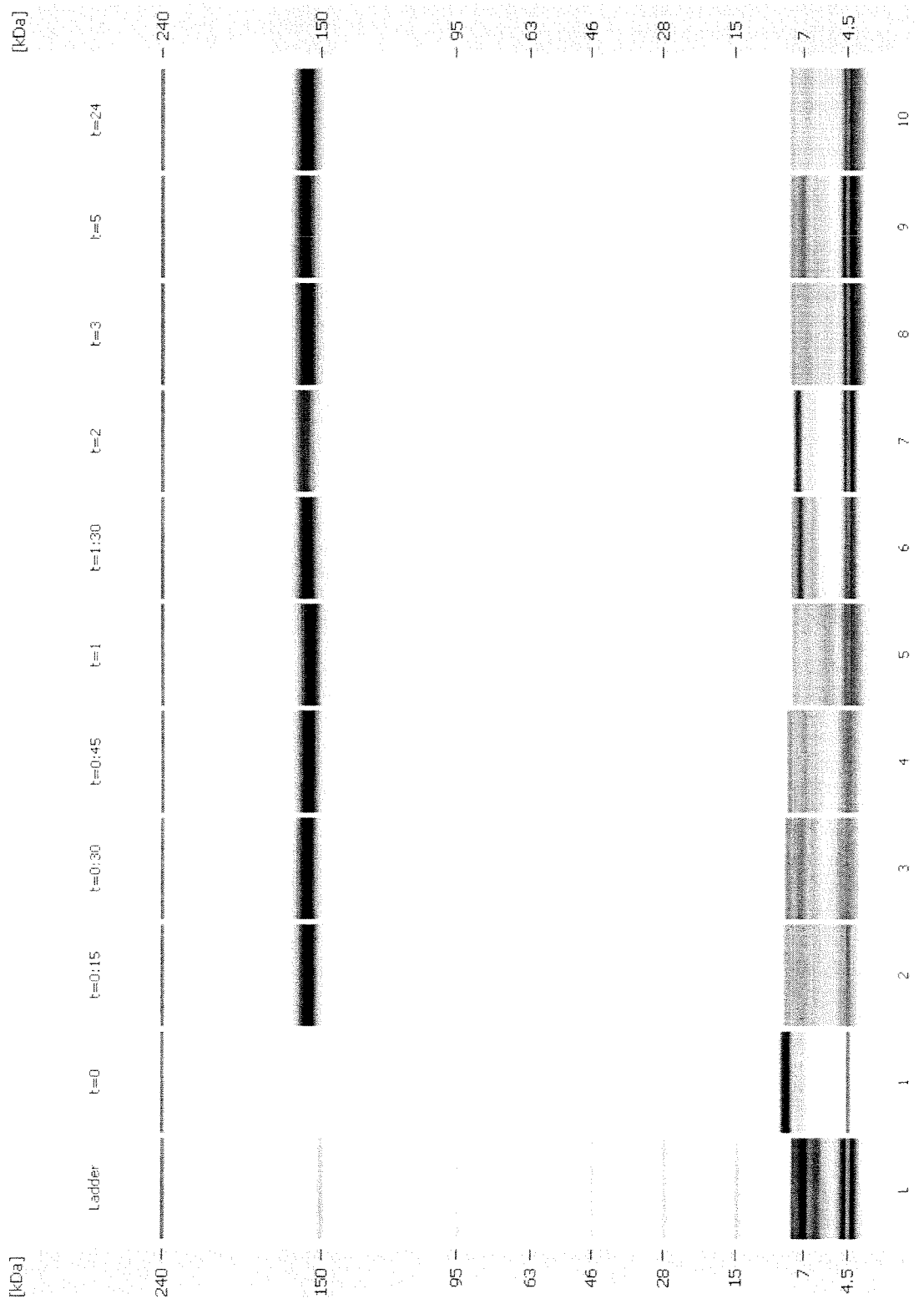

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FIG. 32

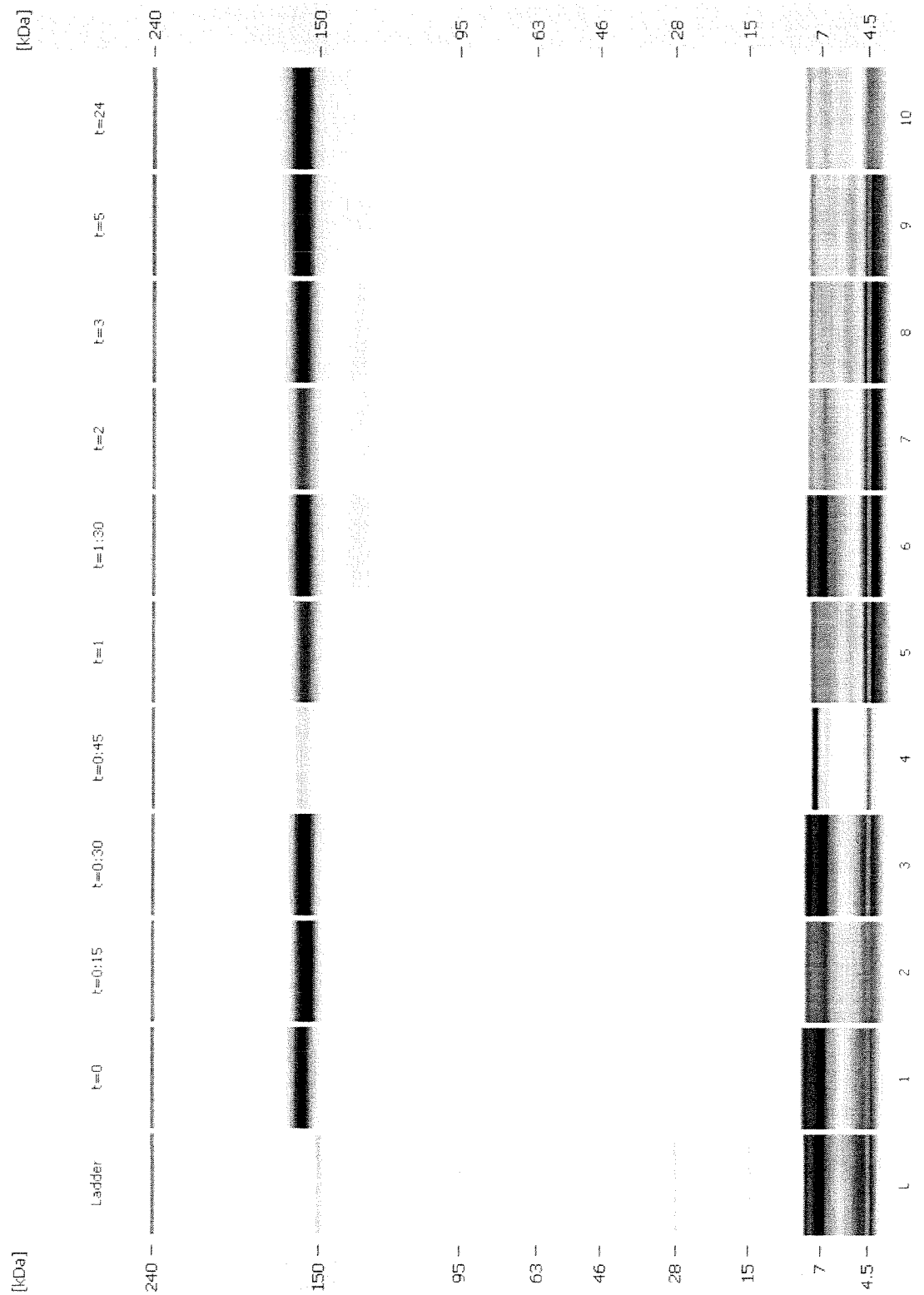

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FIG. 33

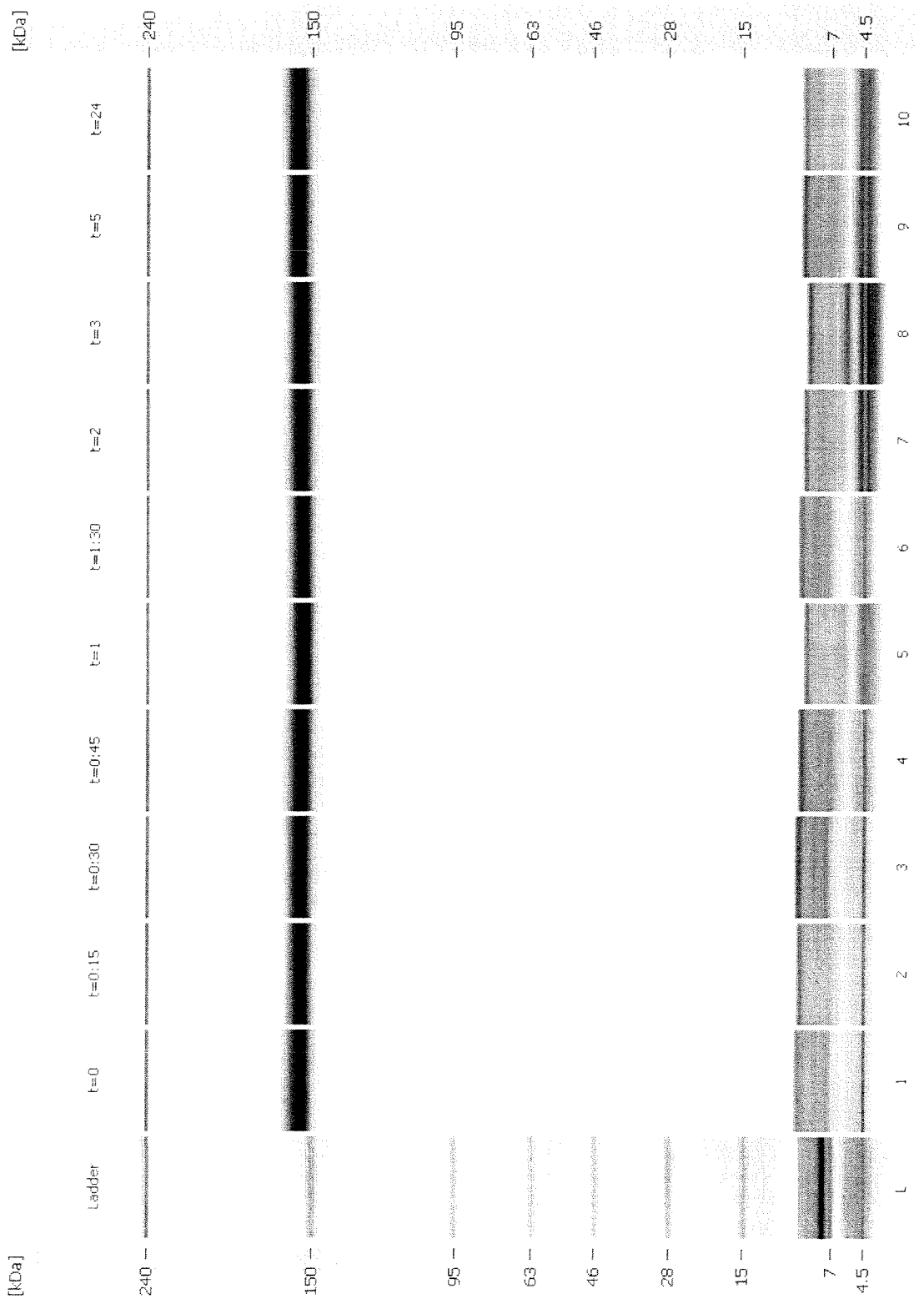

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FIG. 34

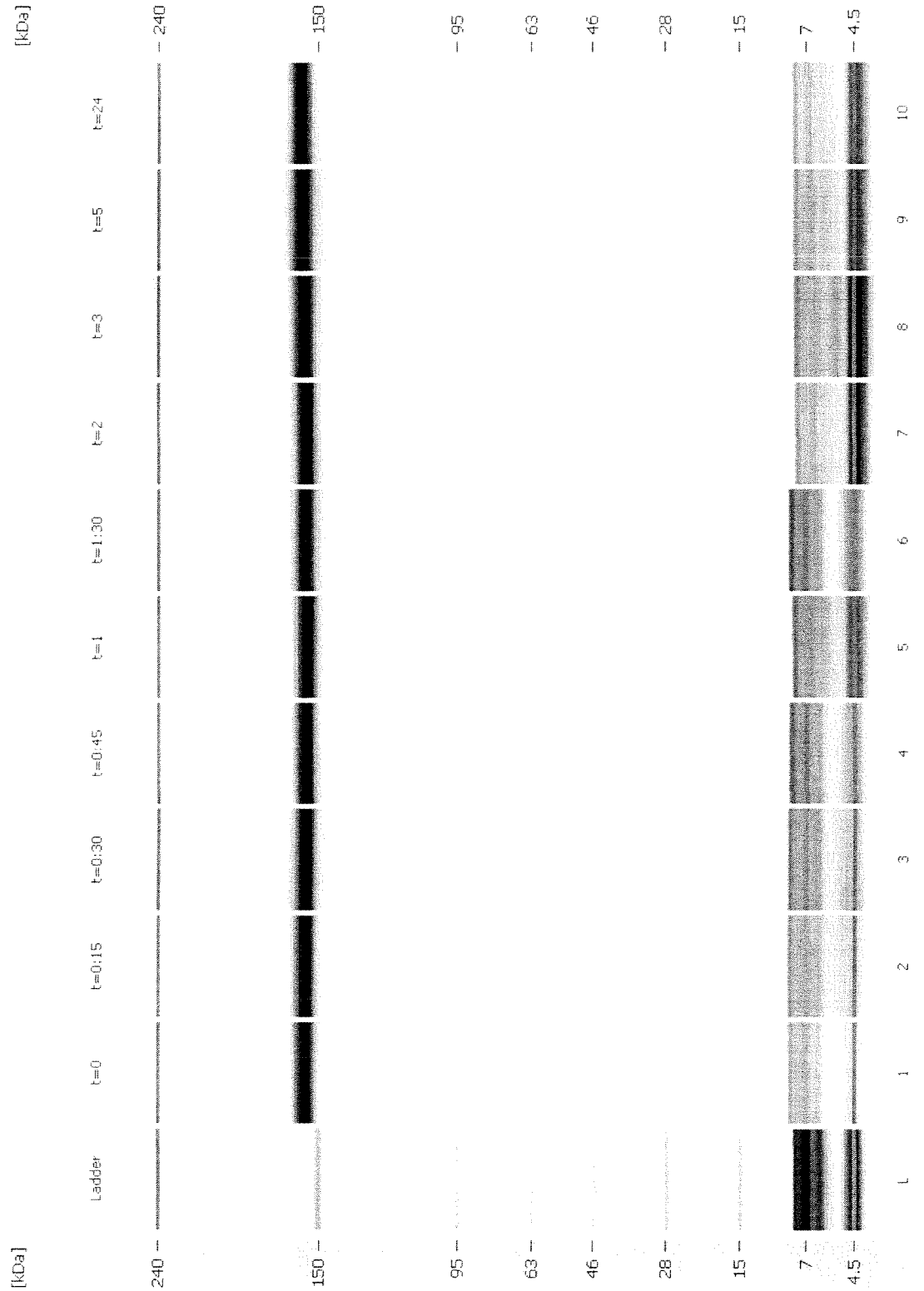

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FIG. 35

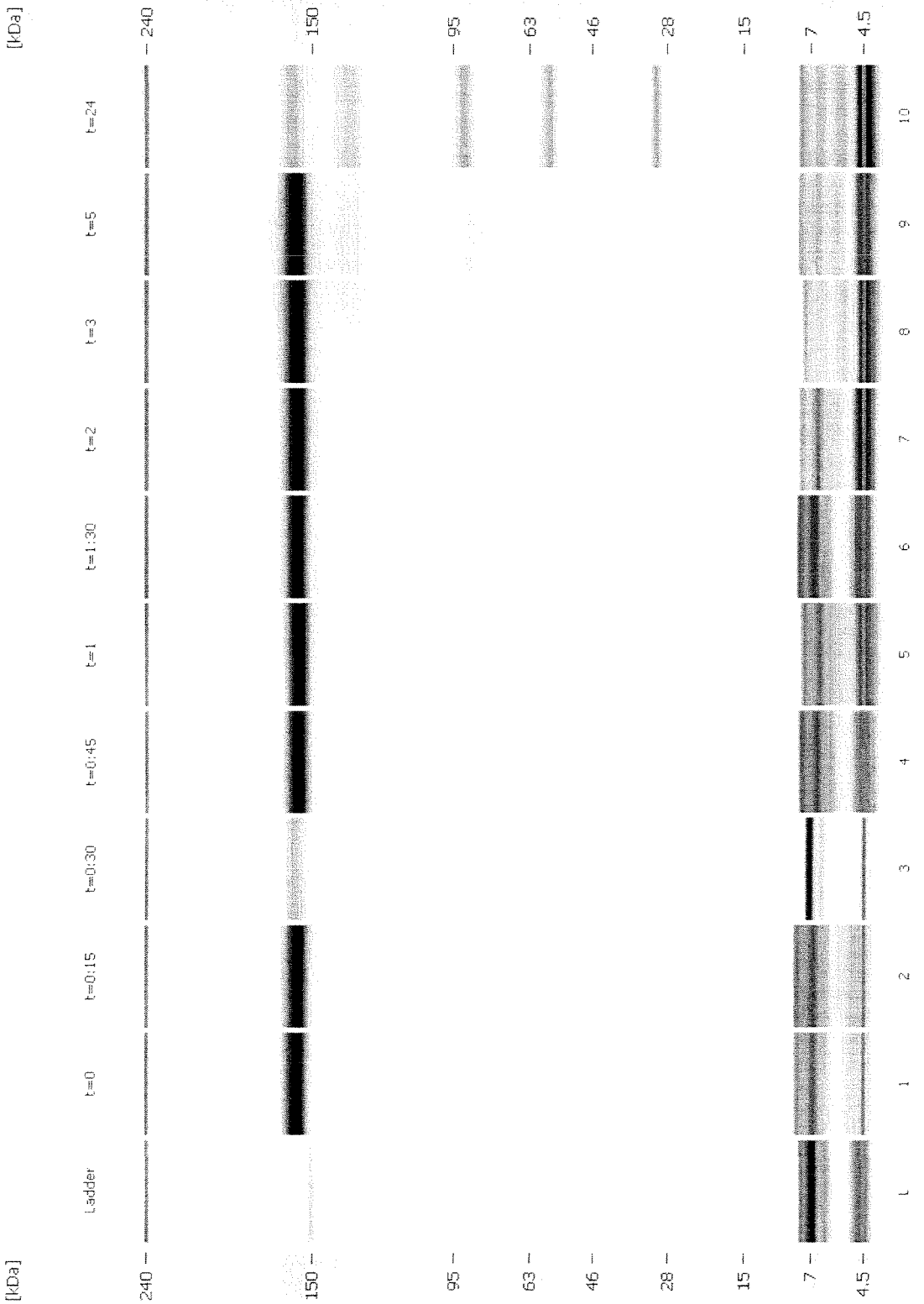

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FIG. 36

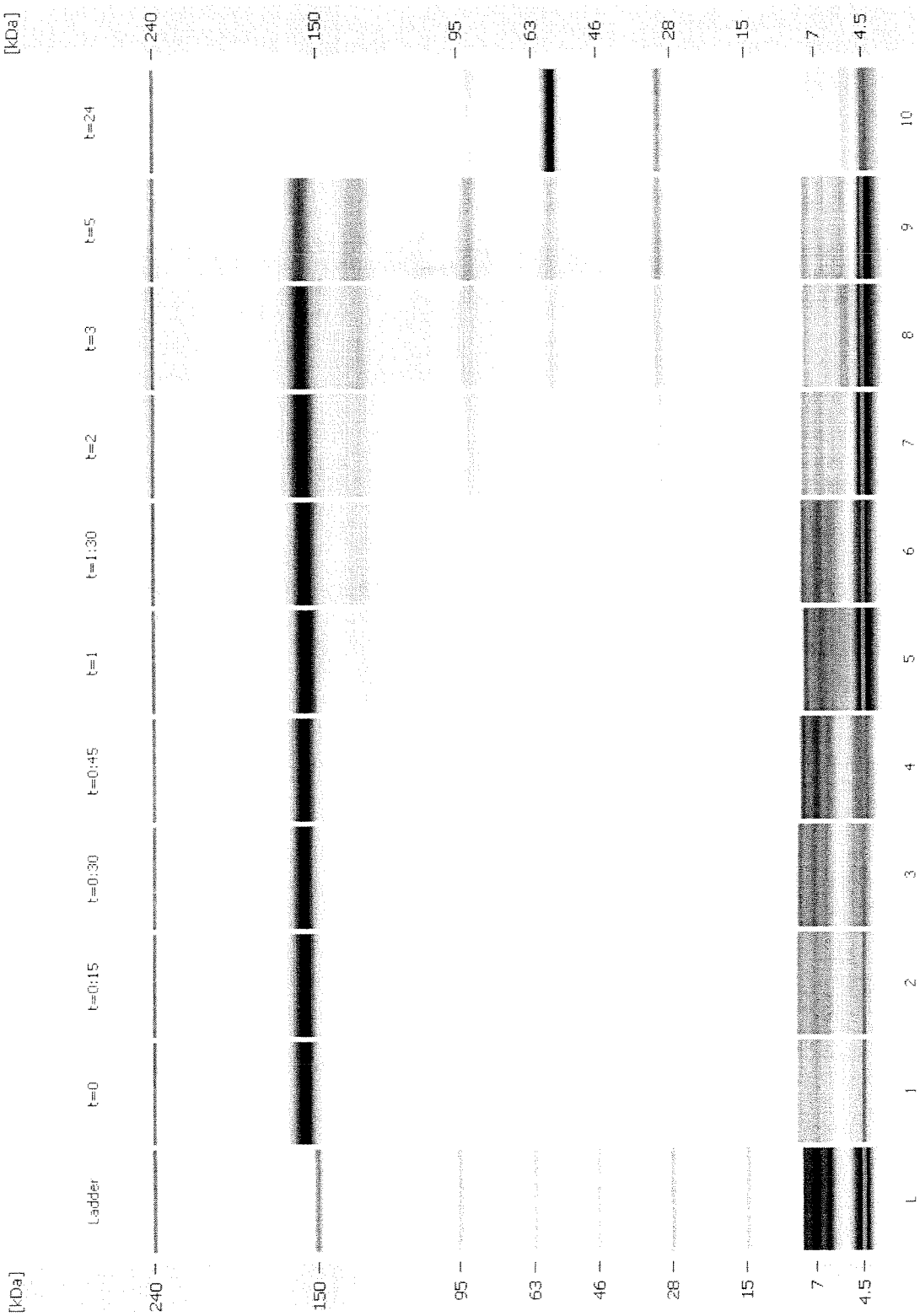

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t=0:15
t=0:30
t=0:45
t=1
t=1:30
t=2
t=3
t=5
t=24
240
150
95
63
46
28
15
7
4.5
L
1
2
3
4
5
6
7
8
9
10

FIG. 37

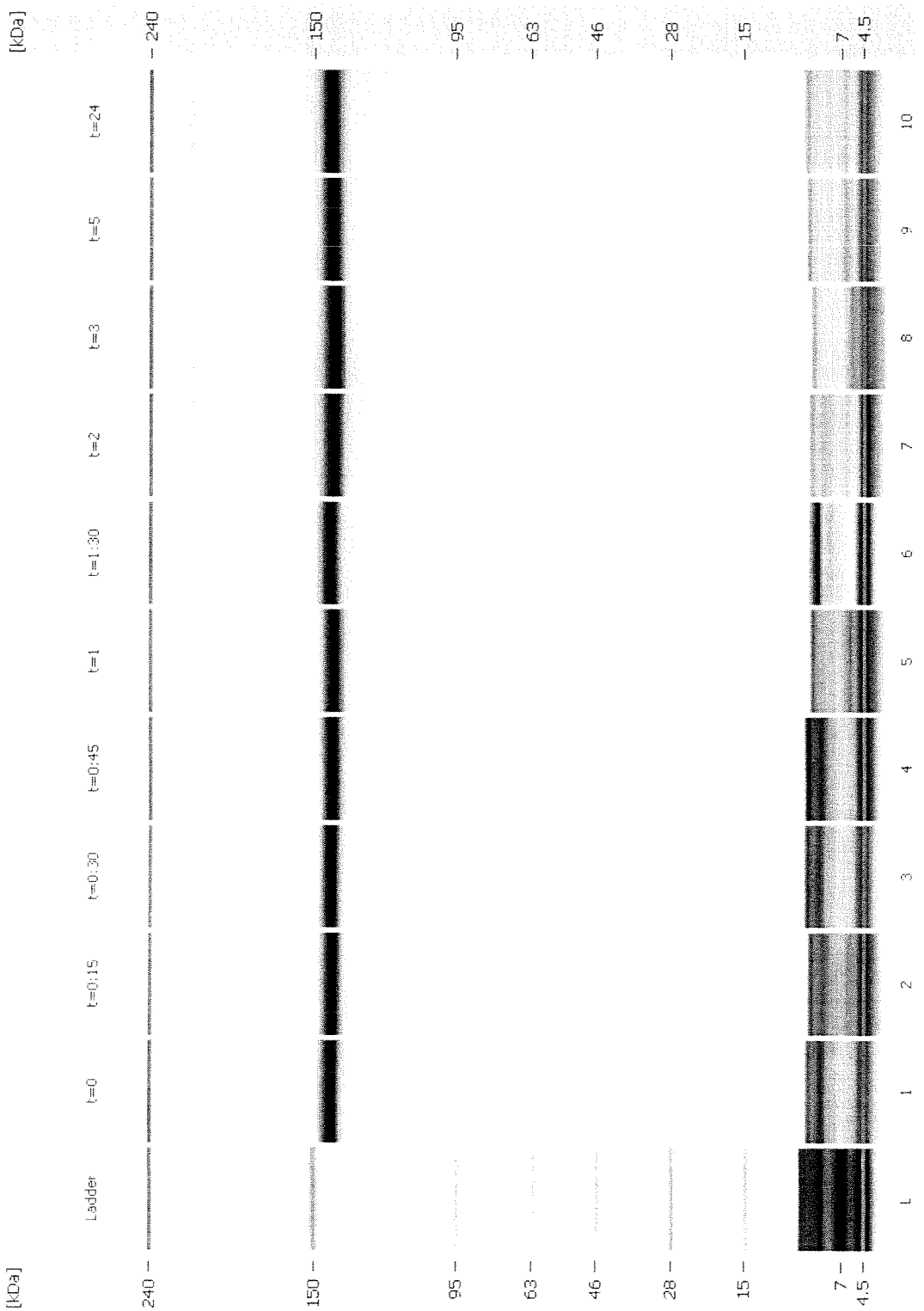

[kDa]
Ladder
t=0
t=0:15
t=0:30
t=0:45
t=1
t=1:30
t=2
t=3
t=5
t=24
240
150
95
63
46
28
15
7
4.5
L
1
2
3
4
5
6
7
8
9
10

FIG. 38

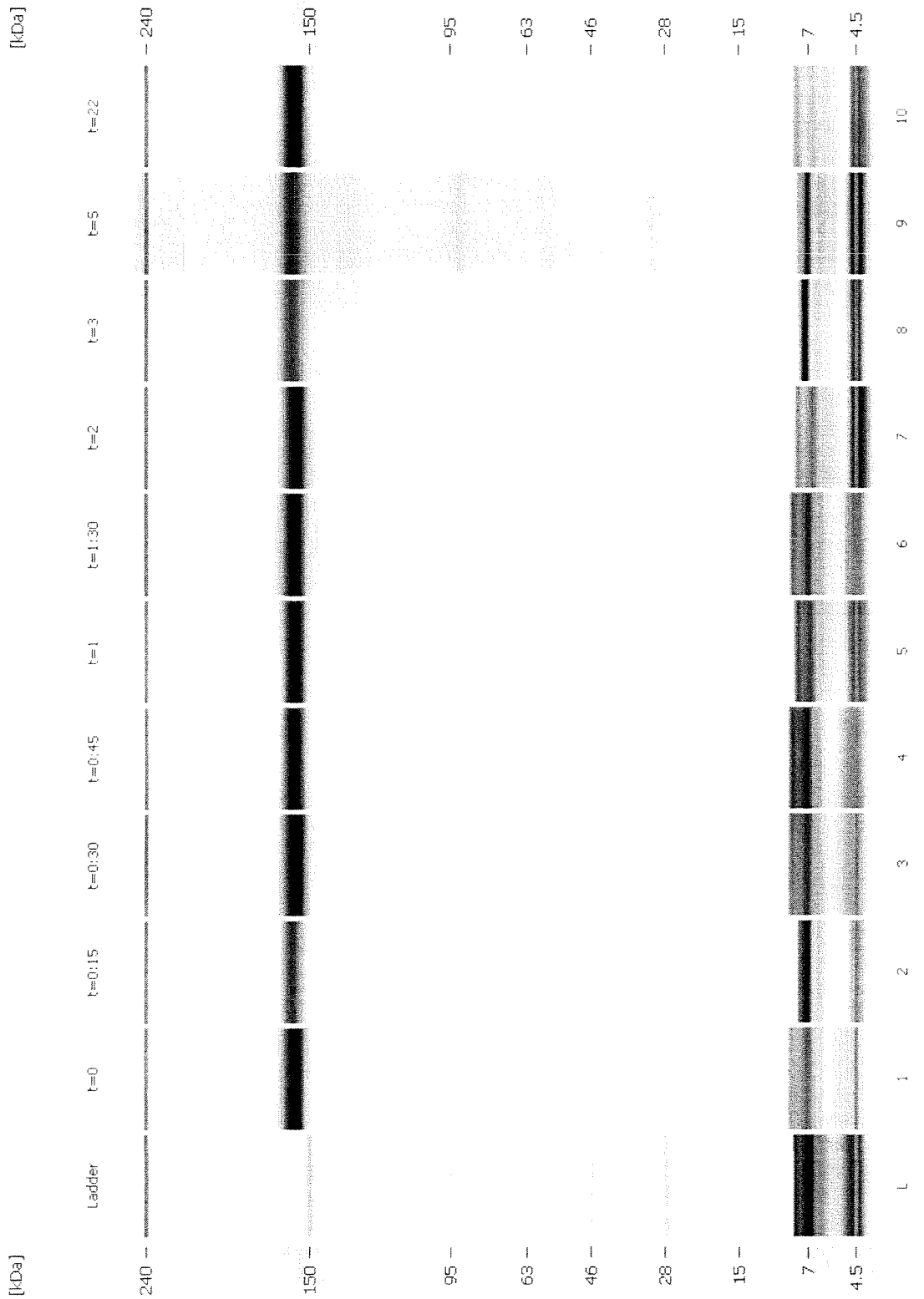

[kDa]
Ladder
t=0
t=0:15
t=0:30
t=0:45
t=1
t=1:30
t=2
t=3
t=5
t=22
240
150
95
63
46
28
15
7
4.5
L
1
2
3
4
5
6
7
8
9
10

FIG. 39

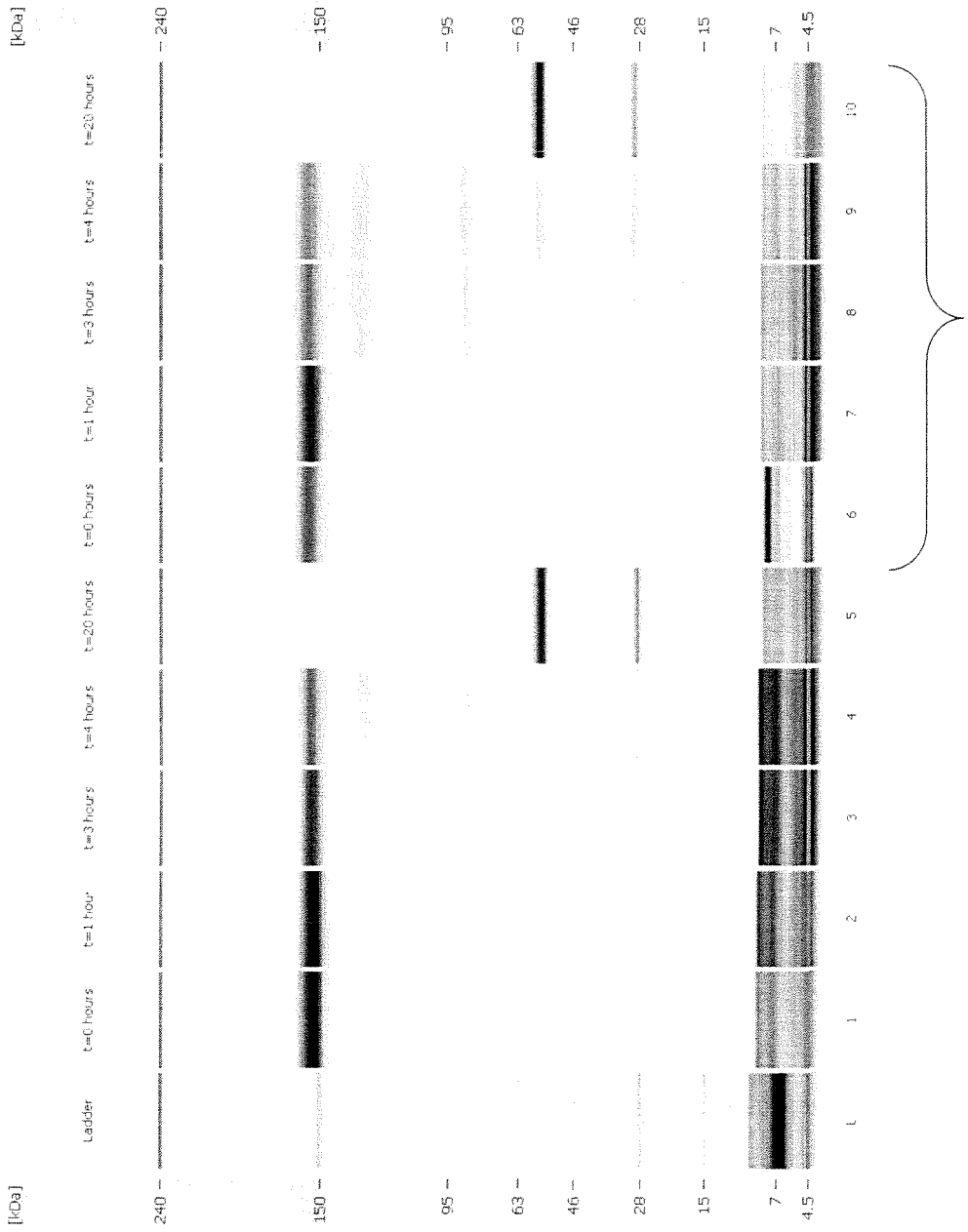

[kDa]
Ladder
t=0 hours
t=1 hour
t=3 hours
t=4 hours
t=20 hours
t=0 hours
t=1 hour
t=3 hours
t=4 hours
t=20 hours
240
150
95
63
46
28
15
7
4.5
L
1
2
3
4
5
6
7
8
9
10
+ 0.1 mM DHEA

FIG. 40

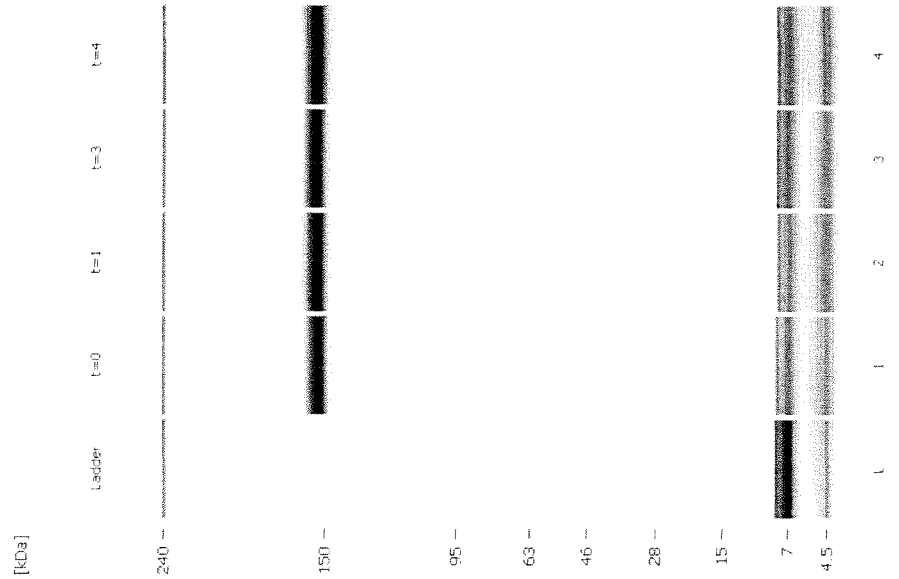


FIG. 41